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J. U. & C. G. LLOYD
CINCINNATI, OHIO

REPRODUCTION SERIES, No. 6.

HYDRASTIS CANADENSIS

Facsimile, reprint and illustrations
of the article in

DRUGS AND MEDICINES OF
NORTH AMERICA

1884

By J. U. & C. G. LLOYD

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INTRODUCTION.

In 1884, under the title "Drugs and Medicines of North America," a quarterly publication was undertaken in Cincinnati by John Uri Lloyd and Curtis Gates Lloyd, the design being to comprehensively study American drugs, historically and otherwise, making a record thereof, in such a way as to be of use to present readers, and of increasing value as a reference record in the future.

To this object a corps of authorities in scientific directions embracing botany, medicine, pharmacy and chemistry, united their efforts, altogether voluntary. Among these special contributors in the opening number are to be found the following names: Prof. Roberts Bartholow, M. D., LL. D.; Prof. Virgil Coblentz, M. A., Ph. G.; Prof. E. M. Hale, M. D.; W. E. Hallowell, M. D.; Prof. J. A. Jeançon, M. D.; Prof. John King, M. D.; Mr. J. A. Knapp, Artist; Prof. F. W. Langdon, M. D.; Prof. F. B. Power, Ph. G., Ph. D.; Prof. A. B. Prescott; Dr. Charles Rice, Ph. D.; Prof. Eric E. Sattler, M. D.; Prof. Robert Sattler, M. D.; Prof. J. M. Scudder, M. D.; Prof. John V. Shoemaker, M. D.; Mrs. Louisa Reed Stowell, M. S., F. R. M. S., and Prof. Robert R. Warder.

To the efforts of these and such as these as special subjects opened their avenues, may be ascribed the high position that the publication immediately assumed in the scientific and professional world.

No efforts were spared to comprehensively present each subject, the plan being to commence with the Ranunculacæ, considering however only those plants having a record in medicine. From the Prospectus we extract as follows:

"It will be neither a Medical nor a Pharmaceutical Journal; but a serial devoted exclusively to the subject indicated in the title. All these journals will welcome it as an ally."

The first number of this 32-page quarterly appeared in April, 1884, with a frontispiece of *Clematis virginiana*, and the publication was continuous until June, 1887, (Vol. II, No. 5) when, owing to the press of business and the interest then being taken in library directions by the undesigned, it was discontinued. The publication as stated embraced Volume I and Nos. 1 to 5 inclusive of Vol II.

Among the drugs exhaustively considered, historically and otherwise to that date (1885), was *Hydrastis canadensis* (then only of Eclectic importance), the study extending from page 76 (October, 1884), to page 184 (June, 1885). Since that date, this drug has become of international importance, and there is an increasing demand for the *Drugs and Medicines* publication carrying this article. But this has long since been out of print, and consequently is not obtainable even for library purposes.

The Lloyd Library has therefore reproduced the aforesaid article on *Hydrastis*, and herein presents to its exchange list a verbatim print, with full illustrations, as it originally appeared in *Drugs and Medicines of North America*.

Respectfully,

THE LLOYD LIBRARY.

Cincinnati, June 1, 1908.

HYDRASTIS CANADENSIS.

GOLDEN SEAL.

PARTS USED.—The rhizome and rootlets of *Hydrastis canadensis* Linn.

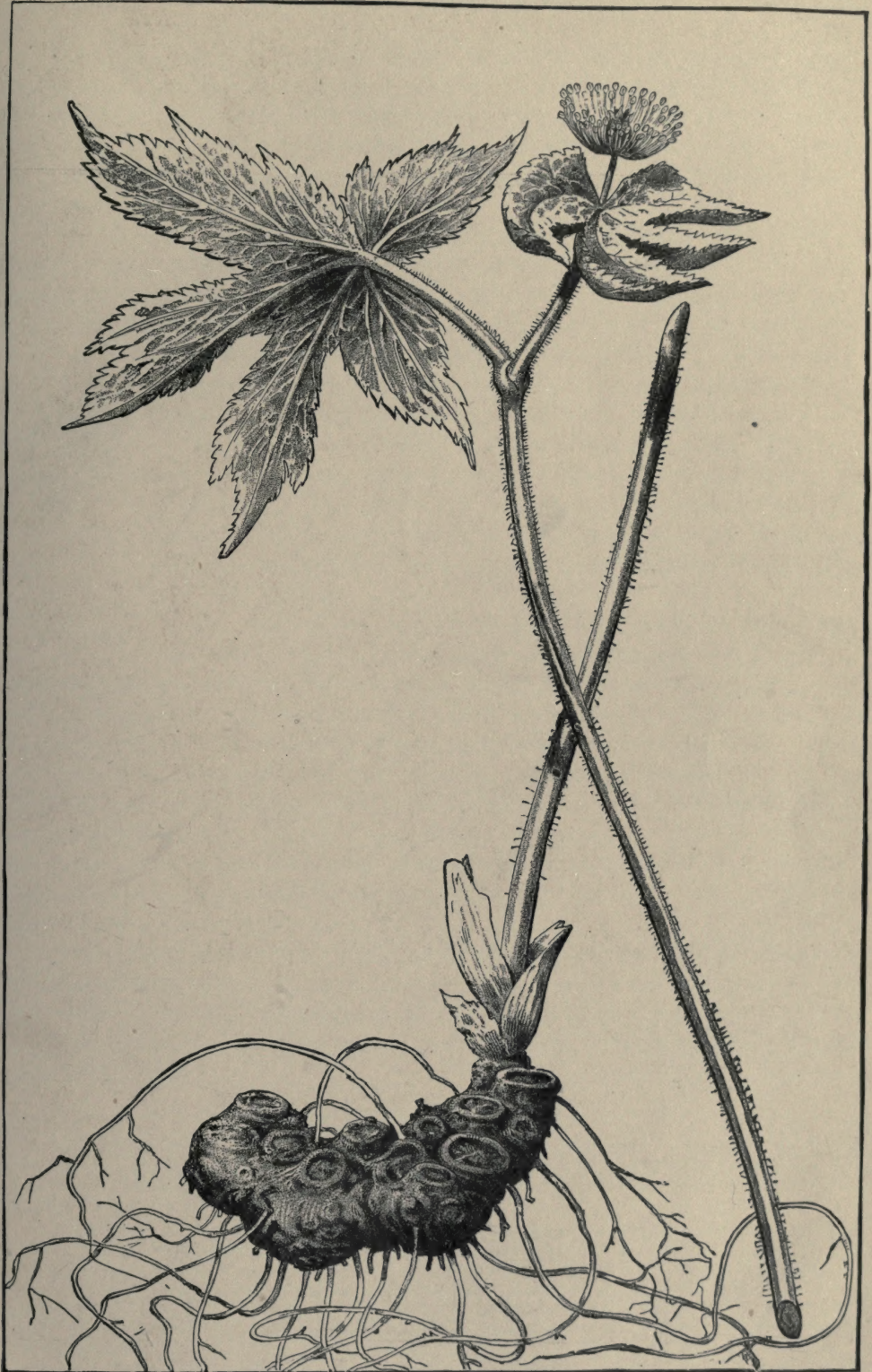
Natural Order Ranunculaceæ, Tribe Helleboreæ.

BOTANICAL ANALYSIS.—Rhizome knotted, horizontal, with fibrous roots. Stem, from six to twelve inches high when in flower, about a foot high when mature; erect, round, sparingly hairy, with short, somewhat appressed hairs; surrounded at the base with two or three yellowish scales. Leaves, two, alternate, roundish-cordate, five or seven palmately lobed, veiny; margins, doubly serrate: Lower leaf, the larger, on a petiole one to two inches long; upper leaf, sessile. Flower solitary, erect, terminal, on a peduncle from a half to an inch long. Sepals from two to four, generally three, round, concave, greenish white, caducous. Petals none. Stamens numerous, spreading; filaments thickened upward, white; anthers adnate, dehiscing longitudinally. Pistils, ten to twenty, in a head; ovaries one-celled, two-ovuled. Fruit, a head of fleshy carpels, each containing one or two small, black, hard seeds.

COMMON NAMES.—The Pharmacopœia (1880) has adopted, and we think wisely, Golden Seal as the common name for this plant. In commerce the drug is known either as Golden Seal or Yellow Root. The name Golden Seal is very applicable to the plant, and has reference to the seal-like scars on the rhizome, and its golden or yellow color. The term was introduced by the Thompsonians, and is largely used by the drug trade, especially by Eclectic houses. Yellow Root is also applicable, and is also a common name for the plant in commerce. Unfortunately, however, it has been applied to several other plants: One of them, *Xanthorrhiza apiifolia*, is an article of commerce under the name. On this account it would be better if the name Yellow Root, as applied to *Hydrastis*, should be discontinued in favor of the Pharmacopœial name. In addition to these two names, a number of local names have been given the plant. In botanical works it is usually called Orange Root or Yellow Puccoon. When in fruit the plant resembles an herbaceous *Rubus*, and hence is called Ground Raspberry. It was formerly reputed valuable as an eye-wash, and in old works the name Eye-balm and Eye-root are given to it. From the yellow coloring matter, and the fact that it was used as a yellow stain by the Indians, it has received the names Indian Paint, Yellow Paint, Indian Dye, Golden Root, Indian Turmeric, Wild Turmeric, Curcuma, Ohio Curcuma, Wild Curcuma (spelled in old works Kurkuma), Jaundice Root and Yellow Eye.

BOTANICAL DESCRIPTION.—*Hydrastis* grows in patches in rich, open, hilly woods. The stem is produced from a terminal bud of the perennial rhizome. Its growth is very rapid: a week or ten days' continuance of warm weather in May is sufficient for it to grow six inches high and to expand its flower. At the base the stem is surrounded by a few yellow bud-scales, and the color of the underground portion of the stem, and for about an inch above the ground, is light yellow.

In a patch of *Hydrastis* will be found, in about an equal number, two kinds of stems, sterile and fertile. The sterile stems bear only a terminal peltate leaf. In reality these sterile stems are radical leaves, with the articulation at the base of the petiole.



HYDRASTIS CANADENSIS.

The fertile stem is from six inches to a foot high at flowering time, round, erect, and about an eighth of an inch in diameter. It is naked below, and at the top apparently forks, one branch bearing a leaf, the other a smaller leaf and a flower. In fact, the stem bears two alternate* leaves and a terminal flower, the lower leaf on a stalk about two inches long, and the upper leaf sessile at the base of the flower stem.

The leaves at flowering time are only partly developed: the lower is larger, measuring from two to three inches in diameter; the upper, which is about half as large, encloses the flower in the bud, and is generally but partially unfolded when the flower opens. After the plant has flowered, the leaves grow to be six to eight inches in diameter. In shape they are roundish cordate, and have five to seven palmate lobes. The veins are very prominent on the lower side of the leaf.

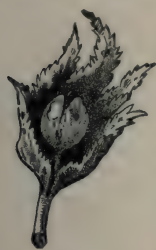


FIG. 27.
Flower bud of *Hydrastis canadensis*.

The flowers are small, white, and last but a few days. A patch of *Hydrastis* will not remain in blossom longer than a week or ten days. The sepals are only seen in the bud, as they are caducous, falling away when the flower expands. The numerous stamens have white filaments, and they are the most conspicuous part of the flower.

The fruit ripens in July, turning from green to bright red. The color is of a very rich shade, and is that which is known to artists as crimson lake. It is borne on an erect stalk, about an inch long. In shape it resembles a large red raspberry, with coarse drupes. Botanically it is an *etærio*, viz.: a fruit consisting of several drupes aggregated together. Each fruit consists of from eight to twelve drupes. The drupes contain two, or, by abortion, one, round, black, shining seed, imbedded in a white pulp, which has a sweetish taste. Some of the drupes are generally entirely abortive, and some much more developed than others, giving the fruit an irregular appearance that is not sufficiently shown in our cut (Fig. 28), which was drawn from a very perfect fruit.

BOTANICAL HISTORY.—At the time Linnæus published the first edition of his *Species Plantarum* (1753), he was acquainted only with the leaves of the plant,† and from their resemblance to the leaves of *Hydrophyllum*, he supposed it to belong to this genus, and called it “*Hydrophyllum verum canadense*.”

* The alternate arrangement of the leaves is clearly indicated by the articulation. Plants are also occasionally found with three leaves, all alternate. A three-leaved specimen, sent us by R. H. Wildberger, has the two lower leaves of the usual size and position, the third a small, sessile leaf, placed about half way between the flower and middle leaf, and at an angle with both the other leaves.

† These specimens of *Hydrastis* leaves are still preserved in the Linnæan Herbarium. They were most likely given to Linnæus by Peter Kalm, the Swedish naturalist, who traveled three years (1749–51) in this country. On the sheet containing the specimens, Linnæus has written: “*Hydrophyllum verum canadense, cujus flores non videt.*—P. Kalm.” In this connection it is a little singular that Kalm makes no mention of the plant in his works. He was an excellent observer, and had he known any economic use for the plant, would have no doubt recorded it. At Philadelphia, the only part of his journey where he could have met the plant, it is very rare, and was probably not brought direct to his attention.



FIG. 28.

Fruit of *Hydrastis canadensis*.

A flowering plant of *Hydrastis** was obtained by Linnæus a few years later, and in 1759 he described the genus in *Systema Naturale* (Ed. 10, 1759), giving it the name *Hydrastis*,† and Ellis as authority for the name.

*This specimen, which in the Linnæan Herbarium has no mark to indicate from what source it was obtained, was probably given to Linnæus by John Ellis, who had many American correspondents. The specimen is a small flowering plant, broken off about three inches below the leaf, and is merely marked "*Hydrastis*," in Linnæus' handwriting. That Ellis was the donor of the specimen, we think is probable, because Linnæus gives the generic name, with Ellis as authority, though Ellis had never published any description of the plant.

† The derivation of this name is usually ascribed to the Greek words ὕδωρ, *water*, and δράω, *to act*, in allusion to the medical action of the drug on the mucous membranes. This is, we think, an error, for probably neither Linnæus



MAP SHOWING THE DISTRIBUTION OF *HYDRASTIS CANADENSIS*.

EXPLANATION OF THE MAP.

The explanation of the different shades is as follows:

Section 1st, Heavy Shade.—Territory over which the plant grows abundantly in its natural habitats. This section furnishes all the drug of commerce.

Section 2nd, Much Lighter Shade.—Territory over which the plant can be usually found, but not abundantly. In many parts of this section the plant is extremely rare, but a diligent search in situations suited to its growth will generally result in its discovery.

Section 3rd, Very Light Shade.—Territory over which the plant is generally absent, but occasionally reported from a few localities.

Unshaded Section.—Plant entirely absent.

In the same year (1759), Miller published a good colored figure of the plant, stating, "This plant has been lately introduced from North America by the title of Yellow Root, and the character of its flower and fruit being different from those of all the established Genera of Plants, I have given it the name of *Warneria*,* in honor to Richard Warner, Esq., of Woodford, in Essex, who is a very curious botanist, and a great collector of rare plants."

The name *Warneria*, given to the plant by Miller, was only adopted, as far as we can learn, by Jussieu, who changed it to *Warnera*. That it should not have been generally adopted is, we think, a matter of regret, as it was published the same year as Linnæus' name, and was accompanied with a picture, and also a very accurate description of the plant.

GEOGRAPHICAL DISTRIBUTION.—The area of country over which *Hydrastis* grows abundantly enough to be a commercial source of the drug, is extremely limited. In but four States, Ohio, Indiana, Kentucky and West Virginia, can it be profitably collected. Cincinnati is nearly the geographical center of this area, and the supply of the drug once reached the market through this city. In extreme southern Illinois, southern Missouri, northern Arkansas and central and western Tennessee, there are occasionally localities where the plant is common, but they are hardly of sufficient extent to yield any amount of the drug.

Throughout most of Illinois, northern Indiana, southern Michigan, the southern peninsula of Ontario, and near the base and along ravines of the Allegheny Mountains, the plant is found, but is scarce.

In Pennsylvania and western New York it is sometimes reported, but on every occasion as being extremely rare; and its discovery in most any section of these States is considered a matter of considerable botanical interest.

The plant grows in patches, generally on a hillside, in rich, open woods, where the leaf mould is abundant. It does not grow naturally in prairie countries, sterile soil, or swampy situations.†

Hydrastis has no power to adapt itself to altered conditions of growth. Cultivating the land is sure to exterminate it at once, and even cutting off the trees will cause it to disappear in a few years. It is the common report from all botanists that the plant is becoming scarcer every year. In many places where it formerly grew abundant, it is now reported rare.

DESCRIPTION OF THE RHIZOME.—The fresh, full-grown rhizome (see Plate VIII) is from one and a half to two and a half inches in length, and from one-fourth to three fourths of an inch in diameter. It usually subdivides when it reaches a length of from one and a half to two inches in length, and not

nor Ellis was aware of its medical action. It is probable that Ellis gave this name from what he supposed was its natural situation, from *ὕδρα*, an *imbibing of water*. *Hydrastis* is erroneously described as a bog plant in several old English works; and these statements are probably the cause of Prof. Wood, in as late a work as his *Class-Book*, giving its habitat as "bog meadows."

* This plate and name of Miller's was probably not seen by Linnæus until after the publication of the second edition of his *Species Plantarum* (1762). In Linnæus's private copy of this work, he has written on the interleaf opposite *Hydrastis*, "*Warneria* Mill. ic. 130, t. 285."

† The habitat in Wood's *Class-Book*, "bog meadows," is incorrect.

unfrequently forms knotty clumps. When dry the diameter is from one-eighth to one-third of an inch. The color of the fresh rhizome, both internally and externally, is bright yellow, and the plant could be easily recognized by the bright color of the rhizome. The weight of the fresh rhizome, with attached roots, averages from eighty to one hundred and seventy-five grains, and we found that one hundred and sixty-six parts after drying gave forty-six parts. There is considerably more loss of weight by drying if the root is collected while the plant is succulent and growing, than there is after the fruit has ripened.



FIG. 29.

Dried rhizome of *Hydrastis canadensis*.

The dried rhizome is knotty, contorted, rough externally, of a dull brown color, and considerable soil usually adheres to that which appears in commerce. The young dried rhizome is usually marked by little ridge-like rings, from the sixteenth to the eighth of an inch apart. If it is gathered in the spring of the year, after the plant has commenced to grow, it shrivels in drying, and will be wrinkled longitudinally. Upon the upper side of the grow-

ing rhizome, near the stem, several cup-like projections are usually to be found, and these mark the positions occupied by former annual stems. These give the plant the name Golden Seal. The herbaceous stems are articulated to the rhizome, and easily broken off; hence remnants of the stems are seldom found attached to commercial hydrastis, and after the third or fourth year the scar (seal) often becomes indistinct. After four to six years' growth the rhizome gradually decays at one extremity as fast as it grows at the other, and hence a great age is not accompanied by a proportional increase of size.

The recent rhizome is thickly studded with fibrous roots which are sparingly distributed upon the upper surface, but abundantly upon the sides and lower part. These subdivide repeatedly, and when dry they vary in size from the twentieth to the fortieth of an inch, but when fresh are twice as large. The fresh fibers are from three to six inches in length, and are so brittle when dry that as found in commerce the rhizome is often nearly naked.

A transverse section of the rhizome shows that the central ligneous portion of the roots have their origin about one-third the distance from the surface of the rhizome. When fresh their structure is scarcely visible, but upon drying, the surrounding portions of the rhizome assume a hard, resinous appearance, and bright yellow aggregations are deposited upon the woody fibers.

The fresh rhizome contains an abundance of a bright yellow juice, which sometimes, in drying, assumes an orange-yellow color, and by concentration in certain places near the center of the root, occasionally imparts a reddish hue to the central part of the dried root. Usually, however, the fracture of a dry young root is golden or lemon yellow, and that of the old ones of a decided greenish yellow. When the dried rhizome is kept from season to season, it gradually changes internally to brown, or greenish-brown. This alteration com-

mences at the surface and creeps inward, until after some years, by this form of decay, the yellow principles will have nearly perished, and the drug will have become proportionately of less value.

If dried hydrastis is soaked in cold water, after some hours both the rhizome and roots resume near their natural size and fresh appearance. The freshly broken, dried drug presents a mealy appearance, and upon being magnified a few diameters this surface resembles broken yellow beeswax.

The odor of powdered or crushed hydrastis is peculiar and persistent, adhering for hours to the hands or the clothing of workmen who handle it in quantities.* All parts are bitter, and also impart, when chewed, a persistently acrid, irritating sensation, which is entirely distinct from true bitterness and the principle that produces the acidity occasions an abundant flow of saliva.

MICROSCOPICAL STRUCTURE.—(Written for this publication by Louisa Reed Stowell.)

Rhizome.—The cork upon the outside of the rhizome is composed of from four to eight rows of thin-walled, tabular cells, of a dark brown color, with broken and irregular walls, the outer edge of the cells frequently being darker than the inner. The green layer of the bark is composed of from twelve to fifteen rows of oval, clear white, thin-walled cells of parenchyma, loaded with starch grains, chlorophyll bodies, oil and protoplasm. The corners of these cells are thickened, leaving many little open spaces between the cells. The liber layer of the bark is very similar to the green layer, only that the cells are more compressed, fitting into each other so closely as to leave no intercellular spaces.

The cambium is composed of several rows of brick-shaped or tabular cells, separating the bark from the wood. They are clear white, with exceedingly thin walls, and contain only protoplasm.

The medullary rays are quite wide, and composed of a number of rows of parenchymatous cells, stronger and thicker walled than the cambium cells, and loaded with starch grains.

The pith has the usual appearance of large, hexagonal cells of parenchyma, loaded with starch grains.

The woody bundles between the medullary rays, the cambium and the pith, are not fully developed. There are a few small reticulated cells, with pointed ends, and surrounded with a small amount of prosenchyma and considerable parenchyma. The reticulated cells have quite thick walls, and are not parallel with the surface of the rhizome; so it is quite difficult to obtain a good longitudinal section of them. The prosenchyma is in clusters around the reticulated cells, and is of a bright yellow color.

Starch Grains.—Every part of the rhizome, excepting the cork and woody bundles, is loaded with minute starch grains. These are nearly round, with no

* Our experience is that after twelve hours have passed it will adhere to our clothing so noticeably as to be unpleasant to members of our family.

distinct rings or nucleus, and about 1-4000 of an inch in diameter. Occasionally they are found in groups of three, like the starch grains of sarsaparilla.

Root.—In the center of the root is the woody bundle. It is not perfectly developed, and often four clusters of reticulated cells are placed equal distances from each other. At the very center is found a small amount of wood parenchyma. The cells of prosenchyma found in the woody bundle are short and with thin walls. Surrounding the woody bundle is a single row of parenchymatous cells, with frequently the inner wall thickened like stone cells. This row is slightly tinged with yellow, and closely resembles the nucleus sheath of monocotyledonous roots.

The principle bulk of the root is found outside of the woody bundle, and is composed of simple parenchyma loaded with starch grains. This tissue occupies fully four-fifths of the entire root. On the outside of this parenchyma and surrounding the entire root, are two or three layers of dark brown, brittle, empty cells, closely resembling the cork cells of the rhizome.

All parts of the root, excepting the woody bundle and epidermal-like cells, are equally loaded with starch grains similar to those of the rhizome.

DESCRIPTION OF PLATES X. AND XI.

Fig. A. Cross section of the root of *Hydrastis canadensis*.—*a*, outer row of cells; *b*, parenchyma of the root; *c*, row of cells bordering the woody bundle; *d*, reticulated cells; *e*, central woody parenchyma; *f*, wood prosenchyma; *m*, root hair. (Magnified 75 diameters, and reduced $\frac{1}{3}$.)

Fig. B. Longitudinal section of the root.—*a*, outer row of epidermal-like cells; *b*, parenchyma; *c*, border cells of the woody bundle; *d*, reticulated cells; *e*, wood parenchyma; *f*, wood prosenchyma. (Magnified 75 diameters, and reduced $\frac{1}{3}$.)

Fig. C. Cross section of the rhizome of *Hydrastis canadensis*.—*a*, cork cells; *b*, green layer of the bark; *c*, liber layer of the bark; *d*, cells of the newly-formed cambium; *e*, medullary rays; *m*, woody bundle, with prosenchyma, parenchyma and reticulated cells; *g*, pith. (Magnified 75 diameters, and reduced $\frac{1}{3}$.)

Fig. D. Cross section of the rhizome.—(Magnified 20 diameters, and reduced $\frac{1}{3}$. For reference to parts, see Fig. C.)

COMMERCIAL HISTORY.—*The Early Record.*—Tradition teaches that hydrastis was valued by the North American Indians for a dye stuff, as well as in the treatment of disease. This is accepted by early American writers, and the rich color of its yellow juice renders the statement scarcely questionable, when we consider the value that our aborigines placed on bright colors. It is not always easy to establish authentic support for these accepted traditions, and we have therefore been to considerable trouble in searching the records, in order to discover a commercial value for hydrastis among the natives of America. This we are enabled to present as follows: Mr. Hugh Martin read a paper, October 4th, 1782, before the American Philosophical Society, entitled "An Account of some of the principal Dyes employed by the North American Indians." This paper was published in the transactions of the American Philosophical Society (1793, p. 224), from which we reproduce as follows:

"The Indians dye their *bright yellow* with the root of a plant which might very well be called *radix flava americana*. This root is generally

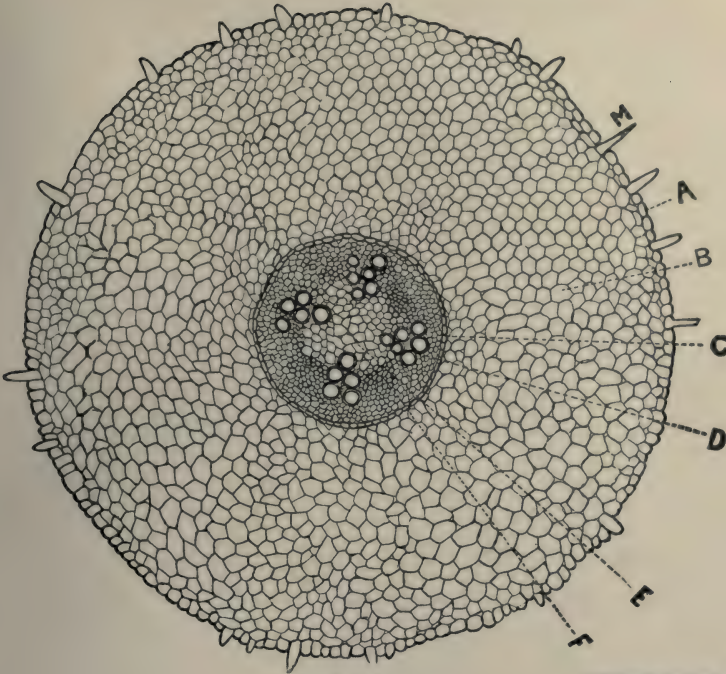


FIG. A.

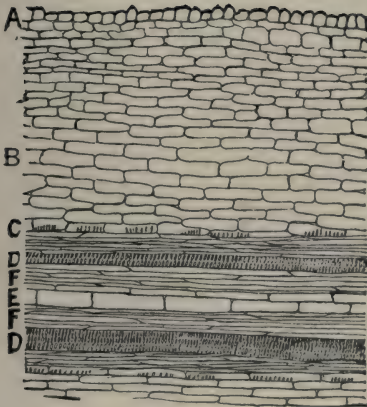


FIG. C.

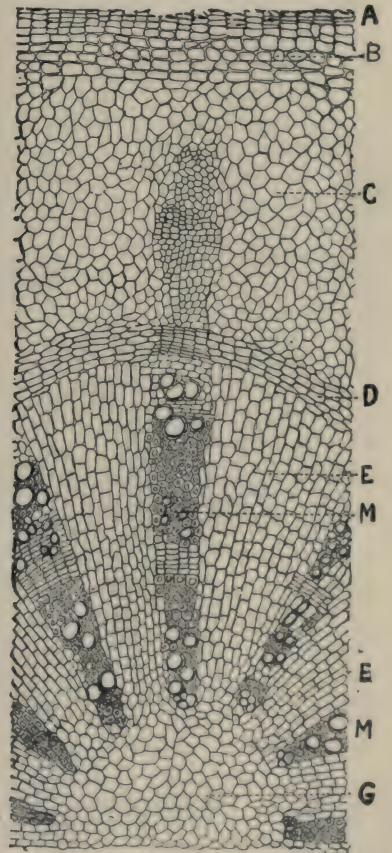


FIG. B.

PLATE XI.

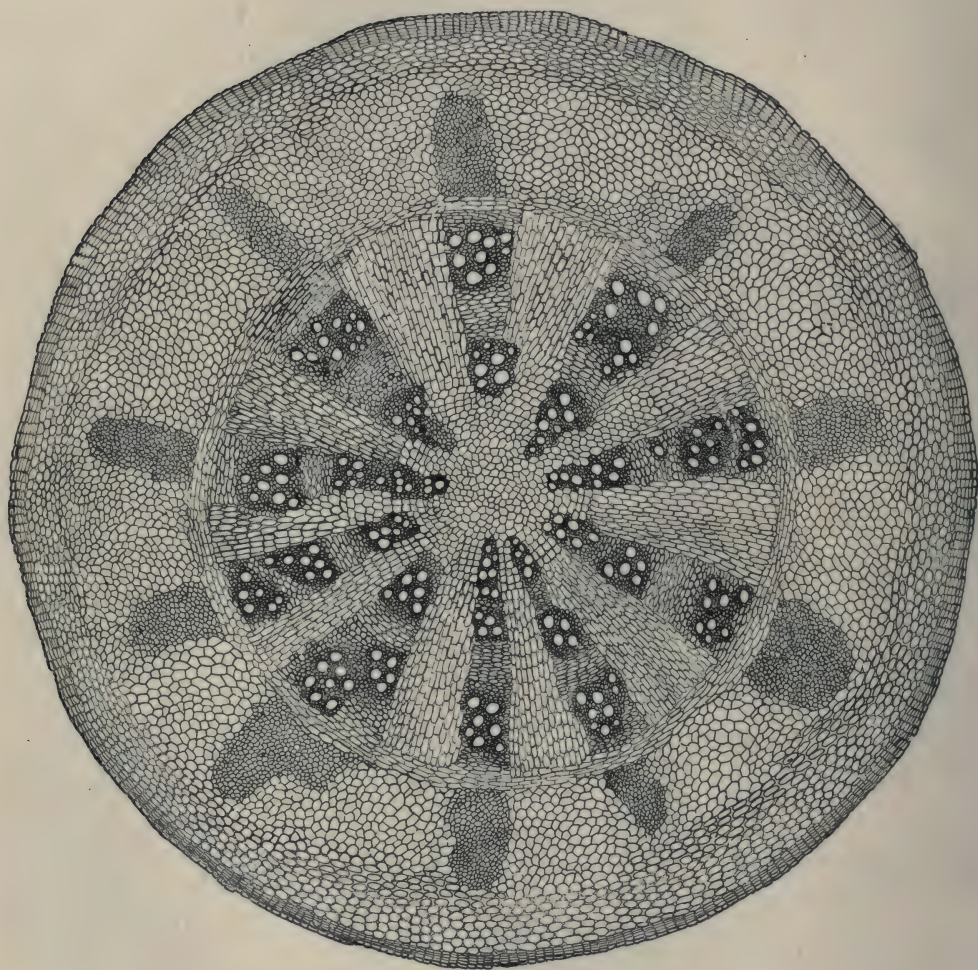


FIG. D.

MICROSCOPIC STRUCTURE OF A CROSS SECTION OF THE RHIZOME OF
HYDRASTIS CANADENSIS.

from one to three inches long, and about one-half an inch in diameter, and sends out a great number of small filaments in every direction excepting upward; these filaments are as yellow as the body of the root itself. From the root there grows up a stalk about a foot from the ground, and at the top is one broad leaf.* A red berry, in shape and size resembling a raspberry, but of a deeper red, grows on the top of the leaf. This berry is ripe in July."

From the time of the Indians until a demand was created for hydrastis by the Eclectics, it was scarcely an article of commerce, but about 1847 (see Medical History and Uses) it became an important drug with those who supplied the medicines known as Eclectic remedies.

In viewing the commercial history of hydrastis, we find that it was scarcer and more expensive in its early day than afterward. The explanation is of interest, as other American drugs are usually found to have similar records. This was owing to the fact that botanists were few, and that there was comparatively little demand for American drugs. In consequence, it became necessary that a higher priced labor should procure the drug at that day than is engaged in its collection at present. Therefore, notwithstanding its abundance and the limited demand as compared with the present day, hydrastis was formerly more expensive than now.

Variation in Supply.—Cincinnati, at that day, was the source of supply for the country, as indeed it largely is at present. When crops are abundant and money plentiful, fewer persons engage in the collection of herbs than during seasons of a failure in produce, or in hard times. In consequence of this fact, the price of hydrastis tends to be greater when the commercial interests of the country are prospering, rather than when there is a depression in trade. This alone will not, however, account for the variation in price as witnessed during the past fifteen years. It is true of hydrastis as with many other of our indigenous drugs, that occasionally, and without any apparent reason, the supplies will be consumed at a season of the year when it is impossible to replace them. This creates an immediate increase in price, and an unwarranted valuation will be temporarily affixed to the drug by those who are compelled to have it. This fictitious price stimulates many persons to collect it who would not do so under other circumstances. The result is that after a few seasons the stock of the country is more than replaced, after which the market becomes glutted. It requires months to make this fact known to the root diggers, and as a consequence they often have a quantity of the drug left on their hands. This they must then dispose of on a market in which there is really no demand, and prices fall to less than the cost of collection. Then the collectors turn their attention to other substances, the hydrastis stocks of the country are gradually consumed, and prices are quiet and regular, until finally it is found that the supply is again exhausted, when "history repeats itself."

* It is only the sterile stems that have solitary leaves. Those that bear fruit always have two leaves. Mr. Martin is a little confused in his statement.—L.

The foregoing record may be modified by circumstances of a local nature, such as the opening of a railroad through a new country ; and in one case we know the market to have been temporarily (locally) glutted with hydrastis from this reason.

It will therefore be seen that with hydrastis the periods of abundance in market are not necessarily connected with the season's influence on the growth of the drug, although a long, wet autumn favors its collection. Indeed, this plant is of slow growth, and the question of its supply in market does not seem to be dependent on a favorable season.

Fluctuations in Price.—In arriving at the statistics herein tabulated, we must call attention to the fact that little dependence can be placed on old commercial prices currents.* Persons familiar with indigenous drugs will recognize the fact that list prices to the consumers of these drugs are not altered, unless some unusual reason exists for making a change.† Therefore we shall give this record from information furnished us by dealers in the drug and our own experience.

About 1844, Mr. Joseph West was a member of the Shaker village near Lebanon, Ohio. He distinctly recalls the early commercial history of the drug, and supports his evidence with figures that give the commercial value of hydrastis between the years 1844 and 1850 at \$1.00 per pound. Dr. T. C. Thorp, of Cincinnati, an early dealer in indigenous drugs, corroborates him in these particulars ; and we are thus enabled to show that at first hydrastis commanded a very much higher price than it has at any subsequent day.‡

The first demand was supplied at a price of \$1.00 per pound, and from that the drug fell to forty cents, and afterward to twenty-five cents. It sold at \$1.00 in 1849.§

In continuing the commercial history, we find that it declined in price until it reached this valuation of about twenty-five cents per pound, which may be said to have been the average price between the period of its fictitious valuation in the early day, and the close of the war.||

After the war the depression in trade that followed caused hydrastis to further decline, until its ruling price was from twelve to fifteen cents, and finally the price paid to the collector was only about eight cents. This did not repay the labor of collection, even to the class of people who dig roots, and the drug

* In the early days hydrastis was mostly in demand by physicians who carried their own drugs, and hence it was not named in regular drug lists.

† The writer has known some of these drugs to be sold for less than cost, rather than change the price temporarily.

‡ There is little use to search elsewhere than about Cincinnati for a record of this drug from first hands at that period. Then Cincinnati was the headquarters for American drugs, and hydrastis especially came into market almost entirely from this city.

§ Mr. West writes us, "Prior to 1846, we dug and sold golden seal root at \$1.00 per pound."

|| Dr. Thorp states that during the war there was a market for all the hydrastis that came into Cincinnati at 25 cents. There was a scarcity in 1867 and 1868, the prices being 50 cents (1867) and 40 cents (1868), as shown by sales of Mr. West ; but this was simply one of the periods of scarcity to which we refer elsewhere.

nearly ceased coming into market.* In the winter of 1867 and 1868 a general demand arose, for it was found that the stocks were exhausted and could not be replaced.† Then an advance followed, and collectors were paid as high as twenty-two cents for a limited period, and in some instances fifty cents (1867) and forty cents (1868).‡ Prices afterward gradually returned to their normal condition, and in 1879 the market was glutted and the warerooms were overflowing. At this period the price became so depressed that commission houses were glad to dispose of the drug for six and eight cents per pound; and we recall one lot of eight thousand pounds that sold in Cincinnati in 1880 at four cents.§

All collection of hydrastis had now ceased, and in 1881 many parties were found without a supply sufficient to carry them to the next season, and that year the memorable drouth that extended over the entire section of our hydrastis producing country rendered its replacement impossible.|| During the winter of 1881 and 1882 hydrastis, in consequence of these combinations, advanced to a figure above anything that it has occupied since 1856, and the crude root sold in lots, when it was attainable, at from thirty-five to fifty cents per pound. The price in a small way was higher, and we recall several sales of from twenty-five to fifty pounds each of powdered hydrastis that commanded seventy-five cents.¶ One stock of twenty thousand pounds was entirely disposed of for not less than thirty cents. During this hydrastis famine consumers resorted to every available method to procure it. Advertisements were placed in the country papers, and even religious newspapers were used to reach the collectors; but of course there was no immediate return, because the drug could not be found and collected in the winter season. The collectors of 1882 received from twenty-two to twenty-five cents at first, but eventually the price

* From 200 to 250 roots of dry hydrastis are required to make one pound, and after paying commissions it can bring but a trifle to the digger at six cents. In our pamphlet of 1878, entitled "*Berberidaceæ of North America*," we describe the people who gather the May-apple, and as the same class gathers hydrastis, we reproduce a portion of that description: "Large amounts from the mountainous and hilly parts of Kentucky and Virginia reach this (Cincinnati) market, from whence it is often shipped in quantities to eastern and other cities. It is gathered by the poorer classes, and regions of country not adapted to cultivation usually furnish the supply. The 'diggers' carry it to the nearest country store and exchange it for groceries and goods. The storekeeper in time accumulates a sufficient amount, sometimes several tons, and consigns the lot to a commission merchant or drug-broker, who disposes of it to manufacturing pharmacists or wholesale druggists. It is usually poorly washed, and is mixed with foreign substances such as trash, dirt, and varieties of other roots; large amounts are shriveled and worthless, being gathered out of season. Such a state of affairs results from the extremely low price of the article; and when we take into consideration the fact that it has paid two commissions and been transferred a hundred miles or more, we can not wonder that the poor digger is careless, or, that the 'root and herb gatherers' are the most distressed of our population."

† Hydrastis should not be gathered before the fruit turns red. After this occurs the plant quickly dies to the ground, especially during a dry season, and soon every vestige of it disappears. Thus it is that when the stock of the country is exhausted, it can not be replaced before the next season.

‡ The house with which the writer is connected was compelled to pay more than double their customary price for some thousands of pounds that had been sent from our city to New York, and we had to freight it back again.

§ This lot sold, in 1882, for thirty cents in New York, and part of it, we are informed, returned to Cincinnati at a higher figure.

|| Members of the American Pharmaceutical Association will remember this drouth. It was the year the Association met at Kansas City, and the journey over the parched plains of what is usually a rich, verdant country will not soon be forgotten by those who made the trip.

¶ The question was not, What is it worth? but, Can you spare any? It must be remembered that the stocks in market really had cost but from six to eight cents, and a price of even twenty-five cents seemed exorbitant. However, these could not be replaced at the old figure for some time.

fell to fifteen and eighteen cents. Notwithstanding the stimulus of these figures, only an average supply was obtained, for with the entire stock of the country exhausted, it was impossible to more than replace it in one season, and the dealers in hydrastis were glad to get it in 1883.* Even now (1884) the price is firm at figures that really are higher than usual. However, the drug is freely coming into market, the small avenues of supply are running into the main channels, and it is not impossible that there will be another surfeit before many seasons.†

The Supply of Hydrastis.—By referring to our map (Plate IX.) it will be seen that comparatively a small section of country produces hydrastis in quantities sufficient for collection. Of this portion, a few narrow channels really produce all the drug of the market. The main source of supply is the country bordering on the Big Sandy river, and the adjacent mountainous portions of eastern Kentucky and West Virginia. Southeastern Ohio, where the country is hilly and broken, also contributes, but not as largely as the portions mentioned of Kentucky and West Virginia. It will be seen that these sections of country are tributary to the Ohio river, and naturally the drug collects in the country stores along the Ohio valley, and eventually much of it arrives in the Cincinnati market by shipment down the river, although some is retained in Wheeling, West Virginia.

Considerable amounts now reach the eastern cities via the Baltimore & Ohio Railway, and since the completion of the Chesapeake & Ohio Railroad through the mountains of eastern Kentucky and West Virginia, a portion of it passes to the seaboard by that line, which also, by means of its connections with the northeastern part of North Carolina, brings to that market a limited supply from the Allegheny Mountains, in the northeastern part of that State. It is estimated by Mr. George Merrell, that of the hydrastis which would ten years ago have all drifted to Cincinnati, but three-fifths now appears in this market, the remainder reaching eastern cities.

The Ohio & Mississippi Railway and the Ohio river carry the hydrastis from southern Indiana (yearly diminishing in amount) to either Cincinnati or St. Louis, although the latter city receives in all but little of the drug.

The sections of country that we have mentioned supply the hydrastis of the world. If the real collecting portions of these States could be placed together, we doubt if the space would occupy more room on our map than the size of the thumb nail. Of course limited amounts occasionally appear in other sections, but these are unimportant and spasmodic. We have consulted every prominent dealer or collector in American drugs in the hydrastis section of the country, and have corresponded with the wholesale druggists in each city

*It must be remembered that one season will not inform all the root diggers that a drug is in demand. Many of them live in mountainous countries, and it is not unusual for them to learn of a demand, then turn their attention to collecting the drug, and finally bring it to market when the demand is over.

†In this connection we must not overlook the fact that liberal advertisements of preparations of hydrastis have had a tendency to create an unusual demand during the past three years. There is no doubt that more hydrastis is now being consumed than ever before.

within and adjacent to the territory. We think that we have recognized every avenue that brings this drug to market, and every section that produces it for market.

The Past and Present Supply.—By consulting our map (Plate IX.), it will be seen that only a small area of country can yield the drug in amounts sufficient to repay collection at present prices, and of this section of country but a limited portion actually contributes any of it to the market. It does not necessarily follow, however, that the plant will not disappear over sections that have never yielded the drug. Hydrastis is so sensitive that even a partial destruction of the timber causes it to shrink away, and one turn of the soil by the plow blots it from existence. If it were like Podophyllum, and content to thrive in woodland pastures, the future would be brighter; as it is, each year witnesses a shrinkage in area and a loss to the world (without economic return) of this peculiarly interesting American plant. It has nearly vanished from the rich hillsides bordering the Ohio river, and is no longer found in quantity in the populated sections of our valley. The more inaccessible portions of broken hillsides must now be drawn upon, and in this view of the matter we find a second in Mr. George Merrell,* who writes us as follows:

"I think the root is becoming scarce, being gathered now, I am told, in small quantities, in isolated places here and there, where in former years it was found growing more like we have seen Podophyllum, in large patches."

In this particular we agree with Mr. Merrell, and from the foregoing view only of the matter we would readily decide that the drug would drop out of market in a moderately near period; however, there is another side of the case.

The mountainous sections of the States we have named can never be cultivated, and they are peopled by a class of inhabitants who barely exist, and who are perfectly content if they only exist. These persons have few expenses, and depend mainly upon the game of their forests and the ginseng and other marketable drugs of their hillsides. The game is becoming extinct, but the nearly inaccessible mountain sides are covered with the virgin forests, and excepting ginseng, with the original luxuriant vegetation and undergrowth. These people are doubtless now turning their attention more directly to our native drugs than ever before, and although the mountainous territory that yields hydrastis is small compared with the United States, it covers considerable area. Over this country these inhabitants and their descendants will ever wander and eke out their existence.† They may dig hydrastis for many decades without exhausting it, for to dig a patch is to leave enough to reproduce itself. They will not have the aid of the plowshare, as was the case when the drug disappeared from the now cultivated Ohio Valley hillsides; and unless some unusual

* Mr. Merrell is a son of the late Wm. S. Merrell, who really introduced hydrastis as a drug into commerce. Mr. Merrell is now the moving spirit of the firm that is the heaviest consumers of hydrastis in the world, and his statistics are particularly valuable.

† Apparently in a miserable condition, in reality happy and contented. To pass through these sections of country is to have our sympathies excited, and unnecessarily. These people ask only to be left to themselves and their mountains.

demand springs up, it is not unreasonable to argue that hydrastis will continue in market as plentiful and as cheap as at present for a generation, perhaps generations to come. This argument is supported by the fact that since the introduction of the drug it has decreased steadily in price, and excepting the periodical scarcity we have mentioned (see *Fluctuations in Price*, p. 90), there has been an abundance of it. The fact that large lots were a drug on the market in 1879, and sold at less than cost of collection (we doubt if any instance preceding 1879 can be shown where as much as 20,000 pounds sold for from four to eight cents), would seem to indicate that the decrease in area is not necessarily accompanied by a decreased supply. The fact is, that the large territory once rich in hydrastis, and now depleted, furnished but a small amount of the drug. The timber was chopped and the underbrush cleared away, without any return. Only here and there did a "root digger" ply his vocation, and great, rich sections of our country, from which the plant is now nearly exterminated, have never furnished a pound of the drug.

Consumption of Hydrastis.—It is usually difficult to arrive at an exact statement regarding the consumption of a drug, but, thanks to dealers and the liberal spirit of manufacturing pharmacists, we are enabled to present statistics that are certainly not far from correct.

The total yearly production of hydrastis will not vary much from 140,000 or 150,000 pounds. We had estimated 140,000 pounds, from statistics furnished by first hands for the drug, and Mr. Geo. Merrell places it at near 150,000.

Of this amount, from 25,000 to 28,000 pounds are annually consumed in making the alkaloids, and the remainder is retailed, powdered, made into pharmaceutical preparations, and exported. It is used in some proprietary medicines, one notably consuming considerable amounts.

Export of Hydrastis.—There is some demand for hydrastis in Europe, although but few of our drug brokers have any European trade in it. From statistics kindly furnished us by exporters, we find that 15,000 pounds were exported in the fall of 1883, but that the foreign consumption is spasmodic. Some of our most prominent jobbers and brokers state that they have never had a call for it from Europe, while others report yearly shipments of from 200 to 1,000 pounds. The demand seems to chiefly come from manufacturing chemists, makers of proximate principles of plants, rather than from those who supply physicians, and we can not find that the drug has been long used in any amount as a remedy in European medicine. During the past year a few contributions to the medical press of Germany and other European countries have directed attention to hydrastis, but the demand that has followed it has, according to our record, mainly been for the fluid extract or proximate principles.

ADULTERATIONS.—The substances which usually contaminate our indigenous drugs, are to be found mixed with hydrastis. Fragments of foreign roots, such as *serpentaria*, *cyripedium*, *senega*, *collinsonia*, *jeffersonia*, *trillium*,*

* We once mentioned this fact, using the name *beth root* instead of *trillium*. As a consequence, we found it

etc., are common, and these admixtures usually result from carelessness of the collector. In a few (exceptional) cases, however, we have found them to constitute more than half the gross weight of several bales of the drug; and under these circumstances the admixtures were intentional.



FIG. 30.
Root of *Stylophorum diphyllum* (one-half natural size).

The root of *Stylophorum diphyllum** resembles *hydrastis* in color when fresh, having a golden yellow juice, but it changes throughout to a dirty gray upon drying. Our attention was once called to a lot of one hundred pounds entirely made up of the root of this plant, which was thrown upon the market as an extra "Large Golden Seal." The appearance of this root will not permit of a confusion of it with the rhizome of *hydrastis*. (See Fig. 30). In our opinion, the color and peculiar odor of dried *hydrastis* will prevent any careful person from mistaking it for the root of any other plant known to us. However, very much inferior *hydrastis* is in commerce, some of it objectionable because of its having been gathered too early in the season, other portions because

of dirt, mould, or admixtures. In consequence of these facts, much of it is unfit for use, and purchasers should exercise care in its selection.

PHARMACOPŒIAL HISTORY.—*Hydrastis* had never been recognized by any Pharmacopœia until it was made officinal in the Pharmacopœia of the United States, in 1860, as "the root of *Hydrastis canadensis*," and then no preparation of it was introduced.

The Pharmacopœia of 1870 continued it under the same name, and authorized the preparation of a fluid extract of *hydrastis*.

The revision of 1880 recognized it as "the rhizome and rootlets of *Hydrastis canadensis*." This revision continued the fluid extract, and introduced a tincture.

CONSTITUENTS.—*Berberine: History of the Name of this Alkaloid.*—In 1824, Huttenschmid discovered a substance in the bark of *Geffroya inermis*, and gave it the name *jamaicine*. This Wittstein (*Organic Principles of Plants*, n. 26) accepts as *berberine*.†

Chevallier and Pelletan discovered it in the bark of *Xanthoxylum Clava Herculis* (1826), and named it *xanthopicrite*, a name that could have been very appropriately applied to this rich, yellow alkaloid.

copied into journals on each side of the Atlantic as *beet* root, a substance that could not well be used as an admixture with *hydrastis*.

*This plant is of interest, and will be considered by us in our publication in its proper place.

†Gmelin overlooked the work of Huttenschmid, and ascribed, in his *Hand-Book of Chemistry*, the discovery of *berberine* to Chevallier and Pelletan. Compare also the statements of J. Dyson Perrins, in the *Journal of the Chemical Society* (1863), and its reprint in the *Pharmaceutical Journal and Transactions* (1863), p. 464.

Rafinesque (1828) named the yellow coloring matter of *Hydrastis canadensis* hydrastine.*

Buchner and Herberger (1830) gave the name berberine to a purified extract of *Berberis vulgaris*, although Brandes previously (1825) may be said to have described a yellow coloring matter that he obtained from this plant.† He did not ascribe a name to it.

Thus it will be seen, accepting all of these substances to be identical, that the name berberine appeared last.

In reviewing the record, we are at a loss to determine why the names that were entitled to the precedence should have been displaced by the term berberine. It may be argued that the words jamaicine and xanthopicrite were not affixed to definite proximate principles, but since the name berberine was originally applied to a solid extract, we can not argue in its favor from that view. The word hydrastine, announced by Rafinesque in 1828, was overlooked by all writers, so that this term could not have entered the lists even had it been known at an early day that this substance was identical with berberine. Therefore the name least entitled to the honor from a chronological standpoint is the term berberine, which by common consent has been accepted.

History of the Alkaloid Berberine.—Authorities have recorded the history of this alkaloid in Europe. Since they overlooked the American history, or were not conversant with it, we shall introduce it, and in connection endeavor to review the entire matter, which can not but be of general interest.

As before stated, Huttenschmid (1824) gave us the name jamaicine; Chevallier and Pelletan (1826) gave us the name xanthopicrite; Rafinesque (1828) introduced the name hydrastine; and finally (1830) Buchner and Herberger announced berberine.

The fact that Rafinesque had entered the lists seems to have then been unknown, and we can find no recognition of him by subsequent investigators; and it seems to us an oversight in passing the work of this eccentric but talented scientist.‡ His "Medical Flora of the United States" (Vol. I.) was written between the years 1816 and 1828, being published at the latter date. In it (p. 253) he defined the yellow alkaloid of *Hydrastis canadensis* as "a peculiar principle *hydrastine*, of a yellow color." We fail to find a better description of this alkaloid until years afterward, for Rafinesque individualized hydrastine, and pointed to it as the prominent principle, by saying of hydrastis, "It contains amarine, extractive, several salts, and a peculiar principle *Hydrastine* § of a yellow color."

* Medical Flora of the United States, 1828, Vol. I., p. 253.

† American Journal of Pharmacy, Vol. III., 1831, p. 173. Also Gmelin's Hand-Book of Chemistry, Vol. XVII., p. 186.

‡ It is true that Rafinesque took the broadest liberties with the sciences in which he wrote, and few will deny that he was very egotistical. However, he was a persistent student, and his works become more valued as the years pass. He entered the field as a writer in several branches of the Natural Science of his day, and it is now recognized that many of those works are among the most difficult to obtain. His "Medical Flora" is rare indeed, and his work upon Fishes is entirely out of market.

§ Italicized by Rafinesque.

We are thus careful in giving this record because the name hydrastine was accepted by a very considerable body of practitioners (Eclectic), and in American commerce it is now hydrastine. *

In continuing the history, we find that in 1830, when Buchner and Herberger announced the name berberine, it was applied to a purified extract of *Berberis vulgaris*. † The substance obtained by them was neither berberine nor a salt of berberine, and the berberine present in their extract could have only represented a small portion of the product. Their process will not admit of any other view of the subject, and the yield of berberine they report, seventeen per cent., can not be obtained from *Berberis vulgaris*. Hence the name berberine was not originally applied to an alkaloid.

In 1835, Prof. Buchner and son obtained, unknowingly, the hydrochlorate of berberine in crystalline form, but thought it a neutral principal, or a weak vegetable acid, and thus we may ascribe to the Messrs. Buchner the honor of really obtaining from *Berberis vulgaris* the first salt of berberine. ‡

Dr. George Kemp, in 1839, assigned berberine to a place among the alkaloids, producing a combination with picric acid. He recorded his experiments in Buchner's *Reportorium*, 1840; but this fact seems to have been overlooked. In 1841 he investigated the substance more thoroughly, producing a hydrochlorate, sulphate, acetate, and some other salts; but in consideration of a request from his friend Prof. Buchner, who wished his (Buchner's) son to re-examine the subject, Kemp withheld his paper from publication. §

Thus it occurred, that in 1847, Thomas Fleitman, unconscious of Kemp's work, published an essay on berberine and its salts, without recognition of Dr. Kemp's labors in the same field. He demonstrated that berberine was neither a neutral coloring matter, nor a weak acid, as the Messrs. Buchner had supposed, but a true alkaloid, and strongly basic. He even examined a portion of the substance made by the Messrs. Buchner in 1835, and supposed by them to be either a neutral principle or a vegetable acid, and found it to be hydrochlorate of berberine. And outside of Mr. Fleitman's report, the testimony from the Messrs. Buchner's description is, in our opinion, to the effect that they obtained hydrochlorate of berberine. They described their product as "A very light powder, composed of acicular crystals, of a bright lemon yellow color, very slightly soluble in cold water." This description will not apply to the alkaloid.

Hence we find that Thomas Fleitman gave to the world (1847) the first general intimation of the basic character of berberine, and he is, therefore,

* When it was shown by Mahla, 1862, that the substance employed by Eclectics was identical with berberine, they (Eclectics) would more readily have accepted the name berberine if it had quietly been announced. Considerable feeling once existed relative to this substance, and Eclectics were not willing to be driven into the use of a name that from their view came after the name hydrastine. But that feeling has passed, and the least said the better.

† Compare *Am. Journ. Pharm.*, 1836, p. 368, from *Journ. de Pharm.*, 1835.

‡ The date of its appearance is variously stated at 1830, 1832 and 1835. Dr. F. F. Mayer refers to Buchner's *Report.* xxxvi., p. 1, 1830, for the original paper (not at our command). See also *Pharmaceutical Journal and Transactions*, 1863, p. 517. We therefore accept 1830 as being well authenticated.

§ *Chemical Gazette*, 1847, p. 209.

accepted by most writers as having assigned it to a place among the alkaloids, although it is established that it had been known by Dr. Kemp to be an alkaloid from the year 1839.*

History of the Yellow Alkaloid (Berberine), as Obtained from Hydrastis Canadensis (1828), Originally Called Hydrastine.—We will again repeat, that in America the name hydrastine was originally given, by Prof. Rafinesque, to this alkaloid, which is the principal coloring matter of *Hydrastis canadensis*, and that he gave it before the name berberine appeared in Europe. By this name it was accepted when introduced into American medicine by the Eclectics (1847), Rafinesque's works being prominently recognized by this section of the medical fraternity. In our botanical history of *Hydrastis* (p. 83), we presume to regret that the appropriate name of Ellis (*Warneria*), was not continued to the plant, instead of the illogical name *Hydrastis*. We also think it unfortunate that, since the name *Hydrastis* was accepted by botanists, it was not followed by chemists in the naming of its prominent constituent, the yellow alkaloid.

No printed process for making the yellow alkaloid (berberine) appeared before 1851, and we must consider that Mr. Durand first announced a salt of berberine from *Hydrastis canadensis*, although he was unconscious that it was a salt. In the year 1850, he wrote a paper on *Hydrastis*, and published it in the *American Journal of Pharmacy*, April, 1851, in which he called attention to "a yellow coloring matter" made by precipitating an alcoholic tincture of the root of *Hydrastis canadensis* by means of a solution of bichloride of tin, describing it as "a most brilliant yellow precipitate." This substance Mr. Durand neglected to investigate, but suggested that it might "prove a useful pigment in oil and water painting." It was hydrochlorate of berberine, and thus he was the first to obtain a salt of this alkaloid from *Hydrastis canadensis* and record the fact.† At this time Eclectic physicians were using the substance as a remedy under the name Hydrastine, or Neutral Hydrastine, and hence it is that the hydrochlorate of the alkaloid was the first definite preparation supplied to the medical profession of America.‡

Although Mr. Durand prepared the hydrochlorate of the alkaloid berberine, in 1850, from *Hydrastis*, and Pharmacists who made Eclectic medicines had supplied it to the medical profession in considerable quantities from before that period, neither had identified it as berberine, or as a salt of that alkaloid, although it was certainly known, by a few, to possess alkaloidal properties.§

* Mr. Fleitman's paper may be found in the *Chemical Gazette*, 1847, p. 129, and following it in a subsequent number, p. 209, the statement from Dr. Kemp, that he (Kemp) had long known of the basic character of berberine, and had remained silent out of respect to the request of Prof. Buchner.

† By a coincidence, the first preparation of the alkaloid used in American medicine was also considered a neutral principle, and in reality was hydrochlorate of berberine. It was called Hydrastine Neutral, being made from *Hydrastis canadensis*.

‡ At first sight it may seem strange that the investigators, without exception, failed to ascribe to this substance alkaloidal properties. It was discovered independently in different plants, by several persons, as our history will show, and in no instance was it identified. Upon deliberation, however, it will be seen that in that early day the alkaloidal tests now so easily applied were unknown. Therefore an alkaloid, forming with hydrochloric acid an almost insoluble salt, was an exception to all known alkaloids, and consequently not likely to be compared with other organic basis.

§ See Grover Coe's work, *positive Medicinal Agents*, 1855. And we refer the reader to our historical introduction of hydrochlorate of berberine for some points in this connection.

Nothing appeared after Mr. Durand's work for a period of twelve years; but in 1862 the subject was taken up by Mr. F. Mahla, of Chicago, and in a paper contributed to the American Journal of Science and Arts, January, 1862, he clearly established the fact, that the Eclectic "Hydrastine" was the salt of an alkaloid, and that this was berberine. Therefore, to Mr. Mahla is due the credit of really identifying as berberine the alkaloid that had been discovered fifteen years previously in *Hydrastis canadensis*.* In this connection we must not forget to record the fact, that Mr. J. Dyson Perrins, of England, really discovered berberine in *Hydrastis* before Mr. Mahla identified it, but he neglected to announce the fact. He states in the Journal of the Chemical Society, 1863, that "sometime before the publication of Mahla's paper, I had noticed the occurrence of berberine in *Hydrastis canadensis*," and thus Mr. Perrins stands in comparatively the same position as Dr. Kemp, both having anticipated the work of the persons who made the announcements.

The Past and the Future Name of this Alkaloid.—It may seem that we overstep the line of prudence, and pass into a field that we should not presume to enter, when we even announce a heading such as the above. We trust, however, that our experience with this almost exclusively American drug, our aggravations commercially, and our endeavor to familiarize ourselves with its past record, will excuse us to the reader, if we cautiously consider the future.

There can be no doubt that the name berberine is applied to the alkaloid by a comparatively small number of American pharmacists and physicians, and that in America the recognized name is still Rafinesque's "Hydrastine." The endeavor to affix the term berberine to this yellow alkaloid of *Hydrastis canadensis*, has as yet proven a commercial failure. It is true, that with scientific men and many writers, berberine is acknowledged, but these men are few, compared with those who use the term hydrastine. The question that naturally presents itself is, are the men who prefer hydrastine entitled to consideration? Although we support the term berberine, we must acknowledge the justice of the name hydrastine from the following reasons:

1. The name hydrastine was applied before the name berberine, the one in America (hydrastine), the other in Europe (berberine).

2. This substance and its salts, under the name hydrastine, hydrastine muriate, etc., came into extensive use in America, and so generally, that at the present day we estimate that from 25,000 to 28,000 pounds of *Hydrastis canadensis* are annually consumed in making the alkaloid and its salts. They are scarcely used in Europe.

3. This name (hydrastine) has become so strongly fixed in the trade interests of our country, that for this reason alone we would even now acknowledge its claims for primary recognition, were *our* country only to be considered.

* We thus see that the American history coincides remarkably with the European, for in 1824 Huttenschmid discovered berberine, and fifteen years afterward Kemp identified it as an alkaloid, although between those periods it had been discovered independently, and examined by several good authorities.

However, even though the name hydrastine is chronologically entitled to preference, and though the amount of the alkaloid produced from *Hydrastis canadensis* for medicinal use, in America, is doubtless very much greater than that from all other sources the world over, we think that the fact of its being familiar to scientists of all countries as berberine, now entitles that word to preference.

Throughout America the name hydrastine is as firmly engrafted as before Mahla (1862) announced that hydrastine and berberine were identical. There is little indication that the term hydrastine will be supplanted by berberine at any immediate day, yet in common with others we have always given our assistance towards bringing about this result. All have failed, and the public seems to tenaciously insist that commercial precedence, and the source of the drug, shall have precedence in the recognition of a name. Hence, in America the name berberine is applied by a few, and hydrastine by the many.

It is not unlikely, however, that if the leaders in the various schools of medicine and in pharmacy will endeavor to bring about uniformity in expression, and will use the word berberine whenever it is possible, it can be made the name of the future.*

Processes Announced for the Preparation of Berberine.—It would be natural to suppose that a substance of the importance of berberine, and studied as this substance has been during a number of years, could now be readily prepared in a state of purity. We will venture to say, however, that according to our investigations, the production of this alkaloid, free from contaminations and decomposition products, is by no means an easy matter. A personal experience of some years on a manufacturing scale by means of the formulas suggested, and accepted by many authors as reliable, has not been at all satisfactory. It is therefore necessary for us to review the processes that have been named; and while we dislike to differ, even in the least, with such excellent authorities as have considered this subject, we must not neglect to add any light that may have been cast in this direction by our work. We find, also, that others have not been altogether satisfied; and investigators who are no less conspicuous in the literature of berberine than Mr. Perrins and Prof. Wm. Procter, have doubted the constitution of the substances produced as berberine. Thus Mr. Perrins states that "the pure alkaloid itself is equally unsuited for analysis. . . . Indeed, I find it not easily prepared in a state of purity." And that Mr. Perrins was uncertain of the substance known to others as berberine, is evidenced by the fact that his ultimate analyses were all made of the salts of berberine. Prof. Procter, in referring to this subject, has written:†

* Few realize the hold of the word hydrastine in America. When we consider that it is applied to a proximate principle that has been used extensively for twenty years, and that the name gives the origin of the drug, we can appreciate the fact that it will be displaced very slowly. There is another argument against the word berberine, and that is the resemblance to *beeberine*. These substances are often confused in commerce, and confounded by physicians, and that they so nearly resemble is unfortunate.

† American Journal of Pharmacy, 1864, p. 10.

“Having occasion recently for information relative to the production of pure berberine in an uncombined state, a reference to all the authorities at my disposal, including nearly all the papers published within the last few years, I noticed with some surprise that these writers, in describing berberine, treated the substance obtained from *Berberis vulgaris* by the agency of neutral solvents, and which, as berberine is an alkaloid, must be a neutral salt of that alkaloid.”

The substance originally called berberine having been found a mixture of berberine and extractive matters, led to the suggestion of several processes for freeing this alkaloid from its combinations. Mr. Fleitmann announced the following: * “Sulphate of berberine was made by decomposing the muriate with weak sulphuric acid; the salt then recrystallized, and dried at 212°F to expel all traces of muriatic acid. Baryta water was added to the solution until it became alkaline, when the liquid immediately assumed a dark red color. To remove the excess of baryta, carbonic acid was passed through the liquid, which was then boiled and filtered, upon which the dark red solution was evaporated nearly to dryness in the water bath, and dissolved in ordinary alcohol; the berberine was precipitated by ether, and recrystallized from water.”

This is the process now adopted by most of the authorities we have consulted, but we regard the product as uncertain and by no means of uniform composition. He first directs the preparation of muriate of berberine, and this salt is then to be dried at a temperature of 212°F . This preliminary step introduces a possible impurity, for we are convinced that such a temperature can not be applied to the moist salts of berberine without risk of partially dissociating them. In this view we find that our experiments have also corroborated those of Mr. Perrins, who writes of muriate of berberine as follows: “I acquiesced in Fleitmann’s formula, and even supposed that it was confirmed by my analysis of the hydrochlorate and by a platinum determination; but later experience has shown me that the hydrochlorate is not suited for ultimate analysis, as by pretty long exposure to a temperature of 100°C ., or thereabouts, it undergoes some decomposition.”

Next, we find that the addition of solution of caustic baryta until an alkaline reaction results, is a procedure that should be avoided if possible, and by no means should the alkali be added in great excess, for the equilibrium of this delicate alkaloid is likely to be disturbed by contact with excess of an alkali. Mr. J. Stenhouse noticed this dissociating power of the alkalies on berberine, and in the *Journal of the Chemical Society, London*, 1867, p. 187, he cautions us against their use, and considers caustic lime preferable to any of them as being less destructive.

Finally, the evaporation of the solution of berberine, after precipitation of excess of barium by a current of carbon dioxide, should not, in our opinion, be carried on at the temperature of a water bath, and most certainly not as Mr.

* *Chemical Gazette*, 1847, p. 129.

Fleitmann directs, "nearly to dryness." Such an application of heat, especially when continued in this manner, will decompose portions of the alkaloid.

Taking these factors together—and we doubt if many workers with this alkaloid will dissent concerning their several influences—we can not but accept that the product must be uncertain. Hence, while Mr. Fleitmann obtained a body which he found to possess certain characteristics, we are not surprised that others who have followed, and excellent authorities, differ both from him and from each other.

In 1862, Mr. Wm. S. Merrell stated that berberine might be prepared by decomposing sulphate of berberine by means of oxide of lead.* Acting on his suggestion, Prof. Wm. Procter elaborated a formula as follows:† Freshly precipitated oxide of lead, basic hydroxide, $\text{Pb}_2\text{O}(\text{OH})_2$, was digested in excess with sulphate of berberine, which had been previously dissolved in boiling water, until a filtered portion of the solution failed to strike a precipitate with solution of acetate of lead or with baryta water. It was then filtered, evaporated and crystallized.

This process seems certainly to be free from some of the objectionable features of those that have preceded, and yet (admitting that berberine can be produced) as a necessity there must be a long-continued application of heat; and this should be avoided.

Again, in our hands the process has been a complete failure in other respects, because it abstracts only a part of the sulphuric acid; and in support of our view we give a synopsis of the following experiments that we have repeatedly made.

One part (480 grains) of nitrate of lead was dissolved in water and precipitated with excess of ammonia water. The basic hydroxide so produced was well washed, and added to a solution of one part (480 grains) of berberine bisulphate ($\text{C}_{20}\text{H}_{17}\text{NO}_4\text{H}_2\text{SO}_4$), in 32 parts of water. The mixture was digested at a temperature of 160°F . for forty-eight hours, with frequent stirring, the evaporated water being replaced, and was occasionally tested with solution of acetate of lead.‡ The sulphuric acid was not withdrawn, the solution giving every evidence of being still a solution that contained a sulphate of berberine. If the liquid be evaporated to dryness, decomposition results; and upon re-solution a deep red liquid is produced, which still contains a sulphate of berberine after the lead is precipitated by means of sulphide of hydrogen. In this case, however, the sulphate conforms to the properties of the normal salt ($\text{C}_{20}\text{H}_{17}\text{NO}_4$)₂ H_2SO_4 .

Under the same circumstances lead monoxide, PbO , fails to withdraw the sulphuric acid from the bisulphate of berberine. We are convinced that Prof. Procter really obtained the soluble normal sulphate as we did with our

* American Journal of Pharmacy, 1862, p. 503.

† American Journal of Pharmacy, 1864, p. 10.

‡ Prof. Procter states that solution of caustic baryta can also be used to determine the absence of sulphate of berberine. We believe that the lead sulphate dissolves to a considerable extent in this solution of berberine; and hence we scarcely think that the barium test is reliable.

ammonia process, a compound that at that time was unknown. In this connection, we remember that Prof. Edward S. Wayne once informed us that in his hands the process was a failure.

In 1867, Mr. G. Stenhouse published in the *Journal of the Chemical Society*, London, a process in substance as follows:*

“One part of acetate of lead is dissolved in three parts of water, and to the boiling solution one part of very finely ground litharge is added in small portions, and heated until the whole forms a thick, pasty mass. This is then diluted with one hundred parts of water, and twenty parts of the finely ground wood is mixed with it and boiled about three hours, and strained. A little litharge is then added to the liquid, and it is evaporated to crystallization, when, ‘on cooling, berberine crystallizes out in dark brown tufts of needles.’

“In order to purify the crude berberine obtained by the foregoing process, it is dissolved in boiling water, and subacetate of lead added as long as any precipitate is produced. This solution, filtered while hot, almost solidifies on cooling to a mass of yellow needles, which, however, still contain lead and organic impurities. They are collected on a cloth filter, pressed, dissolved in boiling water, and sulphuretted hydrogen is passed through it. The hot solution, after filtration to separate the precipitated sulphide of lead which carries down some organic impurities, is acidulated with acetic acid and allowed to cool. The bright yellow needles of nearly pure berberine are collected, pressed, and dried at a gentle heat.”

This process will not produce berberine, but an acetate of berberine. Even if the treatment with solution of basic acetate of lead yielded berberine, it would be impossible to finish the product by acidulating the solution with acetic acid, as Mr. Stenhouse directs, and avoid the formation of acetate of berberine, which is in reality the substance produced by the process. Hence those who employed this formula can not well agree in their description of the product with persons who used the process of Mr. Fleitmann.

Dr. T. L. A. Greve, of Cincinnati, suggested a process in the *Eclectic Medical Journal*, 1877,† whereby muriate of berberine is decomposed by means of oxide of silver. This process certainly produces chloride of silver, with the separation of the chlorine from the alkaloidal salt, and the formation of a substance that dissolves with a deep red color, and which forms salts with acids.

Dr. Greve's plan is to make a boiling solution of muriate of berberine, and add oxide of silver in amount sufficient to decompose it. The reaction we find to be rather violent if moderately large amounts are used, and is accompanied by the evolution of gas bubbles and a hissing noise, even in the small proportions of a few grains. When we consider the unstable nature of oxide of silver when in contact with organic substances, we can not but question the production of pure berberine by this process. The result in our hands seems

* *Journal of the Chemical Society*, London, 1867, p. 127.

† *Eclectic Medical Journal*, Cincinnati, 1877, p. 312.

quite conclusive that oxidation products arise from the action of this powerful oxidizer on the berberine, and that the reaction is not so simple as to be altogether explained by a double decomposition between the two substances.

Lastly, the writer suggested that berberine could be prepared as follows: *
 “Rub eight parts of sulphate of berberine in a wedgwood mortar, cautiously adding ammonia water until in slight excess. Pour the dark liquid into thirty-two parts of boiling alcohol, and allow the mixture to stand thirty minutes; then filter. Stir into the filtrate thirty-two parts of cold sulphuric ether, and cover tightly. Surround the vessel with ice, and allow it to stand from twelve to twenty-four hours; then separate the magma of minute crystals of berberine with a muslin strainer or filtering paper, and dry by exposure to the atmosphere.”

This product is in reality a sulphate of berberine of the composition $(C_{20}H_{17}NO_4)_2 \cdot H_2SO_4$. At the time the process was announced, the writer considered the presence of sulphuric acid to be due to adhering sulphate of ammonium, but subsequent investigations have demonstrated that such is not the case; and the fact was announced in the *American Druggist*, 1884, Sep., p. 166.

After reviewing the published processes that have been brought to our attention, as announced in the foregoing pages, we must admit that this berberine subject is not in a satisfactory condition, and that the contradictory reports of those who have written on the properties of the alkaloid are doubtless mostly due to the variable condition of the product.

The Preparation of Berberine.—Our experiences with the processes that have been recorded having proved so unsatisfactory, and really in accord with the work of others, we have endeavored from time to time to obtain the alkaloid in a state of unquestionable purity. The most satisfactory process, but not by any means without objections, is based on that of Mr. Fleitmann—the decomposition of sulphate of berberine by means of solution of hydroxide of barium.† With the precautions that we suggest, a moderate proportion of a substance can be obtained that conforms to our description of berberine, and which we believe can be accepted as the pure alkaloid.

Make a saturated solution of sulphate of berberine $(C_{20}H_{17}NO_4)_2 \cdot H_2SO_4$ ‡ in distilled water, and at a temperature of 15.5° C. cautiously add solution of hydroxide of barium until in *very slight excess*. Pass a current of carbon dioxide at once through the product, until it ceases to afford a precipitate with a filtered portion of the liquid, and then filter it. Place this dark red solution of berberine in a shallow vessel, and expose it to dry air under a bell glass containing a vessel of sulphuric acid, chloride of calcium, or freshly burned

* J. U. Lloyd, in Proceedings of the American Pharmaceutical Association, 1878. See also *American Journal of Pharmacy*, 1879, p. 11.

† If carbonate of barium would decompose sulphate of berberine completely, the action of an alkali would be obviated. However, it will not do so.

‡ The salt used by Fleitmann and others has been the bisulphate of berberine $C_{20}H_{17}NO_4 \cdot H_2SO_4$. This is so nearly insoluble as to require heat. In order to evaporate the product, heat also is necessary in consequence of its dilute condition. We overcome this by making a cold, concentrated solution of the soluble sulphate.

lime. After the liquid has reached a syrupy consistence, a deep brown crust forms over its surface which is of rather uncertain composition, as it refuses to completely re-dissolve in water. However, deep garnet red, needle-like crystals form beneath it of considerable size, distinct and clearly defined. These bear no evidence of contamination, form salts to perfection, and in our opinion are pure berberine.

This process, it will be seen, presents the following advantages over others:

1st. A very soluble sulphate of berberine is employed, which enables us to obtain a cold, concentrated liquid.

2nd. By close attention the sulphuric acid can be all withdrawn with only a slight excess of caustic baryta, which must be immediately decomposed by means of a current of carbon dioxide.

3d. The final evaporation is without heat; and thus from the beginning to the close of the operation the temperature need not rise above 15.5° C.

Working with very small amounts has not been satisfactory. We prefer to employ not less than a pound of sulphate.

Identity of the Alkaloid (Berberine), as obtained from Hydrastis canadensis and Berberis vulgaris.—The differences in the description of berberine has led some persons to question the identity of the substance as derived from different sources. While it is true that processes that will separate certain salts of berberine from some plants, fail to do so with others, we are convinced that this is in consequence of the natural combination of the alkaloid or the influence of associated bodies. In our hands, after purification, the alkaloid known as berberine is identical in properties, whatever has been its origin. The sulphate, muriate, and other salts of berberine as obtained by us from Hydrastis, conform in character with the same substances made from Berberis vulgaris.

In the year 1862, Dr. F. Mahla, of Chicago, presented a paper* on the substance used by Eclectic physicians under the name Hydrastine.† From the reaction of its salts, and also by the support of an elementary analysis, he decided that it was the well known alkaloid berberine. He believed himself to have been the first to enter this field, for he wrote: "An organic elementary analysis of this substance‡ does not exist;" but at the same time Mr. Perrins, of London, England, was engaged in a similar investigation of the yellow alkaloid of Hydrastis.

Mr. Perrins, after enumerating a number of plants of different natural orders, accepted as indisputable the fact that they all contain the alkaloid berberine. He is undoubtedly our best authority on this subject. He included Hydrastis canadensis, and wrote as follows before entering into the elaborate analyses he made of the berberine salts:§ "It seems unnecessary to

* American Journal of Science and Arts, Jan., 1862.

† See our history of the yellow alkaloid from Hydrastis canadensis.

‡ As made from Hydrastis canadensis.

§ Journal of the Chemical Society, London, 1862, Vol. XV., p. 343.

state in each case from which plant I have prepared the salt for analysis; suffice it to say that the whole of the sources now first announced are included."

Mr. Perrins did not advance his method of comparison; and although there can now be little, if any, doubt that his assertions were based on experimental proof, we feel that our paper would be less perfect were we to neglect the subject.

Therefore we forwarded specimens of perfectly pure and re-crystallized sulphate and bisulphate of berberine to Prof. F. B. Power and Prof. Virgil Coblentz, and to the latter gentleman a specimen of crystallized berberine, all from *Hydrastis canadensis*. These substances were analyzed by Prof. Coblentz, who, after several combustions, assigned to each alkaloid the formula $C_{20}H_{17}NO_4$. Prof. Power made combustions of the bisulphate only, and also reported the empirical formula $C_{20}H_{17}NO_4$. In view of these facts, we think it can be accepted beyond a doubt that the yellow alkaloid of *Hydrastis canadensis* is identical with that of *Berberis vulgaris*, and is berberine.

The Composition of Berberine ($C_{20}H_{17}NO_4$).—The history of the trials through which this alkaloid has passed must be continued to its chemistry. Indeed, it would seem strange if a substance that has gone through so many other vicissitudes should not have met with troubles in this department.

Prof. Buchner (1835) first assigned to berberine the formula $C_{33}H_{18}NO_{12}$ (old notation).

In 1847, Thos. Fleitmann redetermined it from the analysis of berberine prepared by himself, the result being $C_{42}H_{18}NO_9$ (old notation).* He thought that the discrepancy between himself and Prof. Buchner probably resulted from the fact that Buchner examined an impure muriate of berberine. This paper led to a communication from Dr. George Kemp, † who, taking exception to Mr. Fleitmann's calculation, argued from Fleitmann's own analysis that the formula announced could not be correct. He therefore recalculated the formula from the figures of Mr. Fleitmann, and announced that $C_{40}H_{17}NO_9$ (old notation) more nearly agreed with the result of the analysis. ‡ However, from an analysis of the double chloride of berberine and platinum, he obtained the formula $C_{42}H_{17}NO_7$ (old notation).

Dr. Bödeker followed this with a communication to Liebig's *Annalen*, lxi., p. 37, in which, from an analysis of berberine made from Columbo, he agreed with Fleitmann that it is $C_{42}H_{18}NO_9$ (old notation).

Again, Dr. Hinterberger, 1852, from an analysis of the double chloride of berberine and mercury, and Kehl & Swoboda, 1853, § from an analysis of a double salt of cyanide of mercury and muriate of berberine, both agree with Fleitmann's $C_{42}H_{18}NO_9$.

* Chemical Gazette, 1847, p. 129.

† Chemical Gazette, 1847, p. 209.

‡ Gerhardt also noted the discrepancy in Mr. Fleitmann's formula, and proposed the formula $C_{43}H_{19}NO_{10}$. As shown by Mr. Perrins afterward, Mr. Fleitmann's formula was already too high in carbon.

§ Chemical Gazette, 1853, p. 70, from *Ann. der Chem. & Pharm.*, lxxiii., p. 339.

This was the unsettled condition of affairs when Mr. J. Dyson Perrins (1862) contributed his paper on the berberine question.* After reviewing the work of others, he very modestly states that "It is not without some hesitation that I allow myself to question the conclusions of chemists of the eminence of Fleitmann, Bödeker, and others; but my own results are so accordant with each other, the number of analyses I have made, and the variety of combinations I have examined are so considerable, that I feel not only justified in proposing an alteration of the formula, but, indeed, compelled to do so." He argues against Mr. Fleitmann's formula, as others had done, from his (Fleitmann's) own analysis, and says that "the numerical results . . . support the formula I propose rather than his own."

Mr. Perrins then presented the combustion of many salts of berberine, and ascribed to the alkaloid the formula $C_{40} H_{17} NO_8$ (old notation), which is accepted to-day; and we have $C_{20} H_{17} NO_4$ of the new notation.

That this formula is correct, has been settled beyond a doubt. Prof. Ernst Schmidt, of the University of Halle,† states that it is $C_{20} H_{17} NO_4$, as shown from numerous analyses, made of the pure base, the sulphate, hydrochlorate and nitrate; also from an examination of the hydroberberine. And lastly, we call attention to the combustions made by Prof. F. B. Powers and Prof. Virgil Coblentz (p. 105) of the berberine made by us from *Hydrastis canadensis*.

Properties.—‡Berberine crystallizes in tufts of dark brown-red needles, figure 31 representing the appearance of these crystals when slightly magnified. The crust that forms over the surface of the liquid is of a dark brown color. If a concentrated solution of berberine in alcohol be mixed with four parts of sulphuric ether a semi-crystalline magma of an orange yellow color is deposited.



FIG. 31.

Crystals of Berberine,
slightly magnified.

Micro-crystals of this are not so clearly defined and the salt is less soluble than the pure crystallized berberine. In connection with this subject we present (next page) figures 32 and 33, micro-drawings made by Mr. William J. Huck, under the personal supervision of Prof. F. B. Power, of the Department of Pharmacy, University of Wisconsin,§ from specimens of berberine prepared by us in the

manner we have stated. Prof. Power contributes as follows:

"The alkaloid was presented in two forms, as a lemon yellow precipitate (made by precipitation with ether.—Ed.) without distinct crystalline structure, or as a reddish-brown crust, with a darker and somewhat crystalline exterior. Neither of these forms, however, admitted of exact representation, and the crystalline coating upon the crust, after being detached and brought under the

* Journal of the Chemical Society, London, Vol. XV., 1862. p. 339.

† Berichte der Deutschen Chemischen Gesellschaft, 1883. No. 15, p. 2589.

• † The berberine herein described was made according to our process and recrystallized from cold water over sulphuric acid. It responded to all tests for purity, was free from sulphuric acid, soluble in both water and alcohol.

‡ Figures 32, 33, 34, 36, 37, and 38 are all the work of these gentlemen and prepared for our publication.

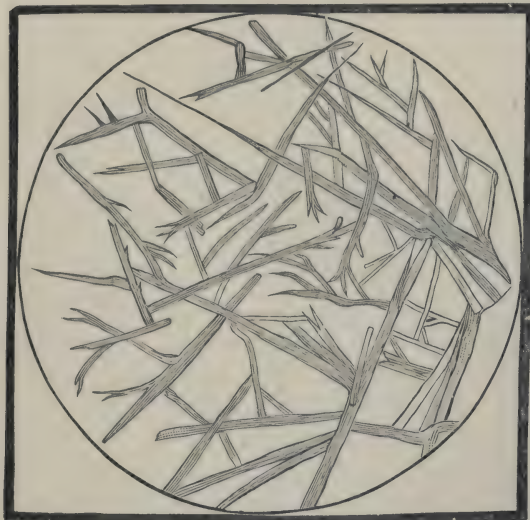


FIG. 32.

Crystals of Berberine (magnified 300 diameters).

microscope, showed such an imperfect aggregation that a drawing would be of little value. To obtain better crystals, both the yellow precipitate and a portion of the dark-colored crust were therefore dissolved in absolute alcohol, and the solutions allowed to evaporate directly upon an object glass.

"Fig. 32 represents the alkaloid berberine as precipitated from alcoholic solution by means of ether, crystallized upon an object glass, and magnified 300 diameters.

"Fig. 33 represents the reddish-brown crust of the alkaloid berberine as crystallized upon an object glass, and magnified 300 diameters.

"Neither of these show a definite crystalline form, while the crystals of Fig. 32 are especially irregular and much branched."

Berberine has a pure and lasting bitter taste and is odorless. It should dissolve without residue in both water and absolute alcohol.

Solubilities. — A reference to our history of the alkaloid berberine will render it unlikely that a name can be applied to so many different substances and these bodies have an accepted solubility. We find, therefore, that the solubility of berberine is stated to be all the way from one part in eighty of water, to one part in five hundred of water. According to our experience berberine varies in solubility in accordance with the proportion of the liquid to alkaloid and time of exposure, and we do

not doubt that even with the same specimens different experiments will obtain discordant results. In presenting the following we will therefore say that a contact of one hundred hours was permitted in a closely-stopped bottle

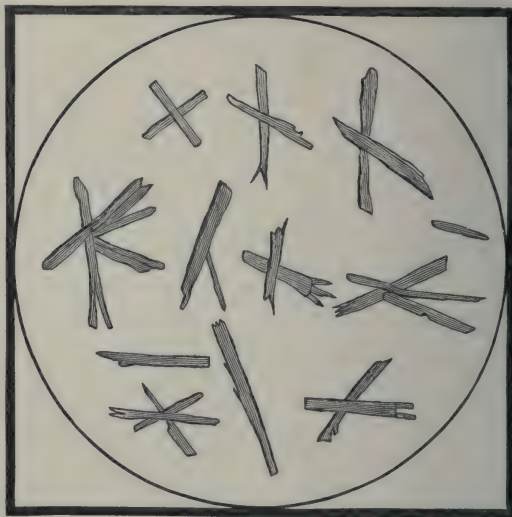


FIG. 33.

Crystals of Berberine, (magnified 300 diameters).

between the liquid and an excess of one-eighth its weight of undissolved berberine at a temperature of 15.5°C . The mixture was shaken frequently, and after perfect subsidence of undissolved matter, the clear overlying solution was decanted, weighed, evaporated at an ordinary temperature by exposure to dry air, and the residue weighed and deducted from the weight of the solution. We used one ounce of berberine in each experiment.

Forty-five and one-fifth parts by weight of the solution of berberine in anhydrous alcohol yielded 6.7 parts of dry berberine.

Thirty-three and one-seventh parts of the solution of berberine in water yielded 1.9 parts of dry berberine. Consequently, one part of berberine dissolved in 6.79 parts of absolute alcohol and in 17.77 parts of water. It readily forms super-saturated solutions with both alcohol and water.

Berberine is practically insoluble in sulphuric ether, chloroform, carbon disulphide and benzol.

Decomposition Products of Berberine.—These are not of great interest to physicians or pharmacists, but we will briefly review the important features of the work that has been done in this direction. Fleitmann found that when berberine is heated from 160° to 200°C . vapors were evolved that condense to an oily liquid, which dissolves in alcohol and is precipitated from such solution by acetate of lead and by water. Hlasiwetz heated berberine in a sealed tube with water, and obtained a substance of a red color and a bronze-like luster by transmitted light, and a green color by reflected light. He added sodium amalgam to a boiling solution of berberine and produced a hydro-berberine of basic reaction of a yellow color and the formula $\text{C}_{20}\text{H}_{21}\text{NO}_4$. This formula has been confirmed (1884), by E. Schmidt,* who states that from its behavior with ethyl iodide, hydro-berberine must be a tertiary base. This author also formed berberine hydriodide by treating berberine with iodide of ethyl; and produced a dibasic acid $\text{C}_{10}\text{H}_{10}\text{O}_6 + 2\text{H}_2\text{O}$, by oxidizing berberine with an alkaline permanganate, which he considered identical with hemipinic acid.

Mr. O. Bernheimer† obtained as volatile products, ammonia and quino-line‡ by heating berberine in a retort with five times its weight of caustic potash. The residue was found to contain two acids which in properties agree with the acids announced first by Hlasiwetz and Gilm. One of these acids was supposed by H. and G. to be protocatchuic acid, and in this connection it is well to call attention to the fact that the alkaloid Hydrastine yielded protocatchuic acid when treated by Prof. B. F. Power with excess of caustic potash. Bernheimer obtained a yellow crystalline mass by heating hydro-berberine with methyl iodide in a closed tube which crystallized in the trimetric system from boiling methyl alcohol. This has the composition $\text{C}_{20}\text{H}_{21}\text{NO}_4$, Me I. and when suspended in water and treated with oxide of silver pro-

*Journal of the Chemical Society, 1884, March, p. 339.

†Hlasiwetz and Gilm suggested that this substance was formed under these circumstances, and Bodeker had also previously announced that distilling berberine with either milk of lime or oxide of lead produced quino-line.

‡Journal of the Chemical Society, March, 1884, p. 340 from "Gazzetta" 13, 342-347.

duced a crystalline hydroxide of the composition $C_{20}H_{21}NO_4, Me HO + H_2 O$. This is strongly basic, liberating ammonia from solution of ammonium chloride. The hydroxide decomposes when heated in a sealed tube, eliminating methyl alcohol. Mr. Bernheimer concluded that hydroberberine is a tertiary base.

The same author found that by heating berberine, mythyl iodide and mythyl alcohol together a methiodide $C_{20}H_{17}NO_4, Me I$, was produced.

On treating this with silver oxide, the corresponding hydroxide was formed, similar in properties to the hydroberberine compound.

Fleitmann announced (1847) that a solution of sulphur in sulphide of ammonium; mixed with a solution of hydrochlorate of berberine, produced a brown-red precipitate of a repulsive odor. This he washed and found still to contain sulphur, but he stated that it did not yield sulphide of hydrogen by treatment with hydrochloric acid. Mr. Bernheimer, upon the contrary, found this precipitate to be decomposed under these conditions with the evolution of sulphide of hydrogen, and the result proved to be hydrochlorate of berberine free from sulphur. He therefore assumes that the precipitate is probably a persulphide of berberine. Hydriodide of berberine ($C_{20}H_{17}NO_4, HI$) was produced by heating hydroberberine with iodine, both being in chloroformic solution. It is soluble in alcohol.

Salts of Berberine.—Berberine is a strong base and unites with acids, forming in many instances most beautiful crystalline salts. These salts of berberine are, as a rule, decomposed by the excess of an acid solution, especially if heated, and hence for example the muriate of berberine forms the sulphate when boiled with diluted sulphuric acid, although under like conditions the alkaloid has a stronger affinity for muriatic acid. It is obvious that the larger number of these compounds are not of interest to our readers, but a few are used in medicine and quite extensively. Some of these have interesting records, and in view of their positions in the history of the alkaloid berberine we were compelled several times to refer to them while considering that alkaloid. In this connection we will say that the early history and pharmacy of these substances has never to our knowledge been presented to the public, and we feel that in these pages it is accurately recorded for the first time.

MURIATE OR HYDROCHLORATE OF BERBERINE, $C_{20}H_{17}NO_4 \cdot HCl$. Crystallized, $C_{20}H_{17}NO_4 \cdot HCl + 2 H_2 O$.—The introduction into American medicine of the salts of berberine was an outgrowth of the introduction of the "concentrations" of early Eclecticism, and intimately connected with it. Therefore, we shall introduce muriate of berberine by the historical connection.

The preparation of podophyllin (Resin of Podophyllum, U. S. P.) in 1847* led to the preparation by similar processes of other materials from *Cimicifuga racemosa*, *Veronica virginica*, *Sanguinaria canadensis*, *Cypripedium pubescens*, and *Hydrastis canadensis*.* All of these substances were first

* See Eclectic Medical Journal, Cincinnati, January, 1849, p. 1, and compare statement of Wm. S. Merrell in American Journal of Pharmacy, 1862, p. 496.

made after the method employed in preparing podophyllin, by simply evaporating the alcohol from a tincture of the respective drug, and then pouring the creamy liquid into cold water. The precipitate, if it were capable of drying, was powdered and sold in that form; but if it was an oleoresin, it was distinguished as a "soft concentration." In an advertisement before us of August, 1852, we note, under the heading of "Concentrations":

"Powders.—Podophyllin, Leptandrin, Macrotin, Myricin, Sanguinarin, and Hydrastin.*

"Soft Concentrations.—Ptelein, Apocynin, Eupatorin, Asclepedin."†

Thus it happened that because podophyllum chanced to yield an active medicinal agent by this method, it was accepted that other similar substances would necessarily prove to be valuable, and Hydrastis was included. However, it was soon found that the precipitate, so-called Hydrastin, neither retained the sensible nor medicinal properties of Hydrastis. It is true that it had a yellow color, and was bitter; but the overlying liquid beyond a doubt contained the valuable constituents of the drug. These obvious facts led to experiments having for their object the separation of the real characteristic principles. After repeated trials, it was found that the addition of muriatic acid to the supernatant liquid (from which the so-called hydrastin had been precipitated) produced a brilliant yellow precipitate, that was very bitter, and seemed to possess the greater part of the sensible properties of the rhizome of Hydrastis. This was introduced into medicine as hydrastin neutral, to distinguish it from the former resinous substance known as hydrastin.‡

The introduction of this second substance inaugurated a confusion in nomenclature that, with the products of Hydrastis, has remained even to the present day. We find the two materials recorded in the prices current of the three principal manufacturers of those times, under three names, to-wit:

MAKER.	RESINOUS PRECIPITATE.	MURIATIC ACID PRECIPITATE.
No. 1.	Hydrastin.	Muriate of Hydrastin.
No. 2.	Hydrastin.	Hydrastin Neutral.
No. 3.	Hydrastin.	Hydrastine.

Thus it is that muriate of berberine was the first salt of the alkaloid used in American medicine, and was at first known by three names. Indeed, it was eventually known by four, because in a short time the resinous precipitate called hydrastin dropped from use, and the term hydrastin became affixed to this substance, muriate of berberine.

Eventually the name hydrastine neutral§ was lost, and this muriate of

* These substances were mentioned by the late Wm. S. Merrell in the Eclectic Medical Journal, Cincinnati, July, 1852, p. 297. We have found no earlier record outside of the discovery of podophyllin by Prof. John King some years previously.

† Afterward the more appropriate term oleoresin was given to the "soft concentrations."

‡ See the first edition of the Eclectic Dispensatory, King & Newton, 1852, p. 214.

§ In those days this term was not so inappropriate. There was no known salt of muriatic acid and an alkaloid, of a practically insoluble nature, and consequently the salt was first thought to be an inactive chemical body which was thrown out of solution by the acid. We also call attention to the fact that Buchner and Herberger obtained the same substance, and regarded it as a weak acid or neutral principle.

berberine remained, for a considerable time, in American medicine under the names hydrastin, hydrastine, and muriate of hydrastine.*

It will be seen from this review of the early history of the substances derived from *Hydrastis canadensis*, that the first definite principle introduced into American medicine was the muriate (hydrochlorate) of berberine. The reader will also note that this was in reality a salt of berberine, for (see our history of the alkaloid berberine) Mahla† demonstrated their identity, and Mr. Wm. S. Merrell immediately accepted the statement of Mr. Mahla regarding the substance that he (Merrell) had sold as hydrastine neutral. In the *Eclectic Medical Journal*, April, 1862, (Mr. Mahla having made the statement in January, 1862,) Mr. Merrell writes: "The fine yellow powder which we have heretofore sold as hydrastine neutral proves to be a true muriate of the hydrastia." He afterwards, in the *American Journal of Pharmacy*, stated that the alkaloid known as hydrastine was identical with berberine. Thus it is that throughout the length and breadth of this country, hydrochlorate of berberine at the present day is recognized as muriate or hydrochlorate of hydrastine, and in this connection we refer the reader to our history of berberine.

The Alkaloidal Nature of Muriate of Berberine.—It is generally accepted that the identification of this substance as obtained from *hydrastis* was first made by Mr. Mahla in 1862 (see p. 99), but in reality he only announced that it was the same as muriate of berberine. It had been placed under the name hydrastine muriate with the alkaloids ten years or more before that, and described in language so expressive, that the definition would be a fair one at the present day. In support of our view of this matter, we quote from "Positive Medical Agents," by Grover Coe, 1855 (written before 1854), as follows:

"*Hydrastine*. This is the alkaloidal principle of *Hydrastis canadensis*. *Hydrastin* is a resinoid which is obtained from *Hydrastis canadensis*. As the reader may wish to know why we name these distinct principles so nearly alike, it may not be improper to give the required information at this point. The resinoids and alkaloids, being clearly distinct, and yet often derived from the same plant, it has been thought best to give the generic name of the plant to the active or concentrated principles, ending them in "*in*" when the active principle is of a resinoid character; and in "*ine*" when of an alkaloid character; thus we have *hydrastin*, a resinoid; and *hydrastine*, an alkaloid."

It will be seen that, while Mr. Mahla announced the identity of berberine with this yellow alkaloid of *hydrastis*, he was not the first to find its alkaloidal nature as obtained from *hydrastis*.‡ In considering the matter further, we

* Afterward another link was added to this unfortunate chain of names by the introduction of "Principles Combined hydrastin." This is a mixture of various substances, and is expected to represent all the peculiar constituents of *hydrastis*. It is now the only substance recognized simply as *hydrastin* or *hydrastine*, these names having, by common consent of manufacturers, been affixed to it exclusively.

† *Am. Journ. Science and Arts*, Jan., 1862, and *Am. Journ. Pharm.*, 1862. p. 141.

‡ See page 98.

note that the nomenclature then adapted agrees with that now recognized by scientists, the alkaloid terminating in *ine*.

Preparation of Muriate (Hydrochlorate) of Berberine.—This salt can be made by precipitating either an aqueous or an alcoholic percolate of hydrastis with an excess of hydrochloric acid. In each case considerable amounts of the impurities are thrown down with the crystalline magma, which can only be completely freed from these associations by repeated crystallizations from both boiling alcohol and boiling water. Therefore it is that we prefer to prepare muriate of berberine from the di-berberine sulphate (by which process no heat is necessary), for it is best to avoid an extended application of heat. If, however, the process adopted be that of the direct production of muriate of berberine from the percolate of hydrastis, a considerable excess of muriate acid is necessary to dissociate the natural combination in which berberine exists, and simply bringing the liquid to an acid reaction, will only throw down a portion of the alkaloid.*

We therefore introduce the following process, announced first by us in 1878: †

Dissolve di-berberine sulphate ‡ ($C_{20}H_{17}NO_{42} \cdot 2H_2SO_4$) in sixteen times its weight of distilled water, and cautiously add hydrochloric acid until in slight excess; drain the precipitate, wash it with distilled water until free from sulphate and muriate of ammonium, and then dry it by exposure to the atmosphere. If desired in crystalline form, dissolve it in boiling alcohol and permit the solution to cool. Hydrochlorate of berberine, made by precipitation, is an odorless, bright, lemon yellow, crystalline powder. When crystallized from hot alcohol by rapid cooling, and then dried, it is in the form of light-yellow, delicate, soft, silky needles, so fine in texture, that a mass of the salt is spongy and cotton-like to the touch. If the crystals are larger, the color is darker, and when of considerable size, they are of a deep orange. Figure 34 (next page) represents a micro-drawing of this salt (prepared by us), drawn by Mr. Huck, under the supervision of Prof. Power, who writes: "Berberine hydrochlorate ($C_{20}H_{17}NO_4 \cdot HCl + 2H_2O$) was mounted in Canada balsam and magnified 60 diameters. The crystals have the form of distinct acicular prisms, and resemble very much in form the mono-berberine sulphate, but are relatively much larger."

Nitric Acid, Action on Hydrochlorate of Berberine.—Fleitmann states that, when hydrochlorate of berberine is added to strong nitric acid, a dark-red solution is formed, and that the application of heat to this solution causes effervescence with liberation of nitric oxide (NO), and that when the nitric oxide escapes, the liquid changes to a lighter color. These statements are supported by our investigations, and we find that if a considerable proportion of hydrochlorate of berberine is used, and the heat continued until the solution changes

* See our remarks under Hale's Third Alkaloid of hydrastis.

† Proceedings American Pharmaceutical Association, 1878. Also American Journal of Pharmacy, 1870, January, p. 11.

‡ At that time we supposed this to be berberine.



FIG. 34.

Crystals of Berberine Hydrochlorate, (magnified 60 diameters).

from dark-red to orange, the liquid will be transparent and syrupy. The liquid which results, mixes with alcohol, hydrochloric acid, nitric acid and officinal ether, but not with chloroform or benzol. With ammonia-water, it forms a dark-red liquid, and this will mix with water. Sulphuric acid also forms with it a dark-red solution, but this quickly changes to orange, with the evolution of gas bubbles. When diluted with water, an abundance of a yellow precipitate (*b*) results, which, when dry, presents the following characteristics: This precipitate is very bitter pulverulent at ordinary temperatures, but falls into a brittle mass when heated. It dissolves in officinal alcohol and ether, (but not in concentrated ether), forming in both instances orange-colored liquids, which stain organic matters yellow. Solutions of the hydroxides of potassium, sodium and ammonium, dissolve it, dark-red liquids resulting, which mix with water and alcohol in all proportions. The foregoing reactions would lead to the inference that this substance might be picric acid, but it is distinguished by the following properties: It is insoluble in chloroform and benzol. Its solutions do not precipitate with solution of ammonio-sulphate of copper, hydroxide of potassium, nor with solution of cinchonine in diluted sulphuric acid; and it gives no reaction with cyanide of potassium. Fleitmann calls it a yellow, difficultly soluble wax. Mr. H. Weidel has studied the oxidation products of berberine, and described berberonic acid, formed by the action of nitric acid on berberine, which can not be identical with this body, as he describes it as colorless, glassy crystals.*

Oxalic acid is another product of the action of hot nitric acid on hydrochlorate of berberine, and this is contained in the filtrate which passes when the precipitate (*b*) is separated. Both Henry and Buchner identified oxalic acid, and Buchner states that he obtained *only* oxalic acid as a result of the reaction. According to our experiments, the oxalic acid is in small amount, but if the proportions of the ingredients are varied, there might be a different result. In addition to the substances we have named, a yellow coloring matter results during the reaction between hot nitric acid and hydrochlorate of berberine, and this is soluble in water, alcohol, dilute acids and dilute alkalis. These decomposition products deserve further consideration.

* We have access only to a summary of this paper, and therefore can not review it as we would like.

Sulphuric Acid, Action on Hydrochlorate of Berberine.—Sulphuric acid dissolves hydrochlorate of berberine with production of a lemon-yellow liquid, which, when heated, darkens, changes to a greenish brown, and finally to dark brown. When the solution of hydrochlorate of berberine in cold sulphuric acid is permitted to stand, it changes to yellowish-brown. There is a difference in statements concerning this reaction, for according to Buchner, the resultant solution is greenish-yellow; Chevallier and Pellatan, red-brown; and Poley, violet-red. Our experiments were made with the perfectly pure salt.

Hydrochlorate of berberine is dissociated when boiled with an excess of dilute sulphuric acid, bi-sulphate of berberine and hydrochloric acid resulting. This was part of Fleitmann's process for making the alkaloid (see page 101). If the amount of berberine hydrochlorate be great, a considerable proportion of the resultant bi-sulphate remains undissolved in consequence of the slight solubility of the salt in dilute sulphuric acid, even if hot. Ammonia water dissolves it immediately, the solution conforming to all the reactions of di-berberine sulphate.

Fleitmann states that the "reddish yellow" solution of hydrochlorate of berberine turns pale yellow on the addition of dilute sulphuric acid, and that the mixture, after a time, deposits delicate, pale, reddish-yellow needles. According to our investigations, a cold saturated solution of hydrochlorate of berberine is greenish-yellow, instead of "reddish-yellow," which latter color indicates the presence of impurities. When acidulated with sulphuric acid, it deposits minute lemon-yellow (instead of reddish-yellow) crystals, which dissolve at once when the liquid is rendered alkaline with ammonia water, thus showing that cold sulphuric acid in excess will decompose muriate of berberine with the production of a sulphate.

Hydrochloric Acid, Action on Hydrochlorate of Berberine.—Cold hydrochloric acid dissolves only traces of hydrochlorate of berberine, but, more freely upon boiling, forming a lemon-yellow liquid. The salt is not decomposed, and it crystallizes when the boiling solution cools.

Acetic Acid, Action on Hydrochlorate of Berberine.—Cold glacial acetic acid dissolves small amounts of hydrochlorate of berberine, and freely when boiling. A crystalline deposit forms when the hot liquid cools.

Hydroxide of Ammonium, Action on Hydrochlorate of Berberine.—Cold ammonia water dissolves small amounts of hydrochlorate of berberine apparently without decomposition, for the solution has the light yellow color of a solution of hydrochlorate of berberine. When boiled with an excess of ammonia water, an orange-colored liquid results, and upon further boiling a slight brownish precipitate is thrown down. It is apparent that the heated ammonia first liberates a small amount of berberine, which dissolves with the orange color, and is then partly decomposed, with production of the brownish substance. Upon cooling such a solution, an abundance of yellow crystals results, which, according to our examination, contain hydrochloric acid, and conform to the reactions of hydrochlorate of berberine. Schaffner states that warm ammonia

water forms a dark brown liquid with hydrochlorate of berberine, from which brown crystals are deposited upon cooling, a reaction we were unable to verify. Buchner and Schaffner supposed that ammonia combined with berberine under these circumstances, but we have not been successful in uniting them.

Hydroxide of Potassium or Sodium, Action on Hydrochlorate of Berberine.—Dilute boiling solutions of these alkalis dissolve hydrochlorate of berberine with liberation of berberine. This is shown by acidulating with sulphuric acid, whereby mono-berberine sulphate is produced. Concentrated hot solutions of these alkalis decompose the berberine, with production of a yellow resinous substance, almost insoluble in water. (See also decomposition products of berberine, p. 109). Hot dilute alcoholic solution of caustic potash acts like the aqueous solution of this alkali.

The carbonates of sodium and potassium, in dilute or concentrated solution, act like the alkalis.

Solubilities.—100 parts of distilled water, with one-eighth part of the undissolved salt, dissolved .204 parts of the hydrochlorate. Under the same conditions 100 parts of officinal alcohol dissolved .400 parts of the salt and 100 parts anhydrous alcohol dissolved .320 parts. It is practically insoluble in ether, chloroform or carbon disulphide.

Incompatibles.—The intense affinity that hot hydrochloric acid has for berberine renders this salt exceedingly stable, and, as we previously stated, led the discoverers to view it as a neutral body, or a weak acid. Consequently, it is not dissociated as easily as other alkaloidal salts. Boiling with excess of the mineral acids displaces the hydrochloric acid with the other. Solutions of the salts of silver decompose it immediately, and this is true of oxide and phosphate of silver, especially at high temperatures.

Hydrochlorate of berberine is mostly precipitated from aqueous solution by the addition of either hydrochloric or nitric acid, and largely, but less quickly, by sulphuric acid. Upon boiling with an excess of these acids, it is dissociated. Its aqueous solution is not precipitated by acetic acid, nor immediately by phosphoric acid (H_3PO_4). The solutions of many salts produce precipitates, among which may be named potassium cyanide (yellow), potassium ferrocyanide (dirty green), potassium chromate (yellow), and potassium iodide (yellow). It is not precipitated by either magnesium sulphate, copper sulphate, or ammonium oxalate.

Solution of picric acid and the soluble picrates precipitate the berberine completely from solution of hydrochlorate of berberine, with production of the insoluble picrate of berberine.

MONO-BERBERINE SULPHATE—BISULPHATE OF BERBERINE $C_{20}H_{17}NO_4 \cdot H_2SO_4$.—This substance was introduced into medicine in America under the name Sulphate of Hydrastine. There are two sulphates of berberine (see di-berberine sulphate and phosphate of berberine), but as this is the one that has always been used under the name, it is the only sulphate recognized in commerce. Its medical value seems to be exactly that of muriate of berberine,

but owing to its more soluble nature, it has nearly displaced that salt from market. Sulphate of berberine has been a favorite with physicians ever since its introduction.

Owing to the fact that this substance can be purified without the application of heat, and that it readily forms a soluble di-berberine sulphate by the action of dilute alkalies, from which other salts are easily prepared, we prefer to make this sulphate, and from it produce the various combinations.

Preparation.—Moisten any convenient amount of powdered hydrastis with officinal alcohol, and pack the powder properly in a suitable percolator which has previously been prepared for percolation. Exhaust the powder with alcohol, conducting the operation until the percolate does not contain enough berberine to repay the expense of manipulation and the loss of alcohol.* Reduce the temperature of the percolate to 50° F. (10° C.), and then gradually stir into it a decided excess of sulphuric acid. The natural combination of the alkaloid will be overcome, and a magma of fine crystals of berberine sulphate will immediately result. Permit the vessel to remain in a cool location for twenty-four hours, and then collect the sulphate of berberine on a filter or strainer of muslin.† Reserve the filtrate for the preparation of the white alkaloid.

The sulphate of berberine at this stage of the operation is impure, being contaminated with free sulphuric acid, sulphate of calcium, a greenish oil which exists to a considerable extent in hydrastis, and with some other foreign substances.

Wash the sulphuric acid from the precipitate by means of cold alcohol; dry the precipitate, and mix it with sixteen times its weight of water; add ammonia water until in excess; allow the solution to stand a few hours, and then filter it. Add to the filtrate a slight excess of sulphuric acid, and collect the precipitated mono-berberine sulphate on a filter. Repeat this operation twice, and then dissolve the salt in boiling alcohol and crystallize it.

Description of Mono-Berberine Sulphate.—Excepting chromate of berberine, this sulphate of berberine is the darkest salt of the alkaloid known to us. When crystallized from a quickly cooled solution in boiling alcohol it forms beautiful groups of acicular crystals which, from their small size, have an orange yellow color. If the solution is less concentrated, and crystallization is conducted more slowly, the crystals are larger and of a deep orange color. When the crystals are of considerable size, an inch in length and an eighth of an inch in diameter, the natural color of the salt is that of a ruby, deeper than bichromate of potassium.

* There can be no regular rule given for operations of this kind. The fineness of powder, packing of percolator, and temperature, influence the process to a considerable extent.

† When a concentrated aqueous extract of hydrastis in large amount is precipitated with excess of sulphuric acid, a finely divided, grainy precipitate of mono-berberine sulphate results. After this has subsided, white, needle-like crystals shoot out from the sides of the vessel and from the surface of the precipitate, which, when collected, washed with water, and dried, present a satin-like appearance. These are sulphate of calcium, and an examination of the precipitated sulphate of berberine, will show it to be largely contaminated with this substance which is also thrown down with it.

From what has been said it will be seen that the size of the crystals will alter the appearance of the salt. This may partly account for the discrepancy which exists in the writings of our authorities. In addition, the application of heat, as we have stated, will change the color, such action being undoubtedly accompanied by decomposition products. If an alcoholic solution be slowly cooled, crystallization commences with the formation of needle-like crystals, which, under certain conditions, will retain their characteristics until they cease to form. Under other circumstances, however, fan-like plates, resembling wasp wings, shoot out in most beautiful clumps, and, finally, perhaps another class of crystals will appear, consisting of granular nodules. These various forms are all sulphate of berberine, modified in appearance by different conditions of the solution and they are not different alkaloidal salts, a supposition once entertained by the writer. Upon separating them from each other, and severally dissolving them, all the modifications may crystallize from each solution, or the needle-like crystals may grow into the fan shape.

Figure 35 represents the micro-crystals of mono-berberine sulphate, prepared by us, and drawn for this publication by Mr. W. J. Huck, under the supervision of Prof. F. B. Power, of the Wisconsin University. They were mounted in glycerine, and were in the form of distinct acicular prisms.

Mono-berberine sulphate is odorless, and imparts to the taste a pure, persistent bitterness, which is devoid of the nauseating properties of such substances as quassia or aloës. When the fine orange-yellow crystals are gently heated, they darken and change to a deep orange, but resume their original hue when the salt is cooled. It dissolves freely in ammonia water, and from this solution the mineral and some other acids in excess throw down precipitates of a salt of berberine and the acid employed. We take advantage of this fact in making other salts of berberine, as before remarked, for it is usually easier and more economical to prepare this sulphate and decompose it, than to prepare the other salts direct from the percolate.

Mono-berberine sulphate crystallizes from both water and alcohol in an anhydrous form. An exposure of eight hours to a temperature of 100° C. does not result in loss of weight. A higher temperature fuses and then decomposes it, a carbonaceous mass remaining.

Action of Reagents on Mono-Berberine Sulphate.—Dilute sulphuric acid,

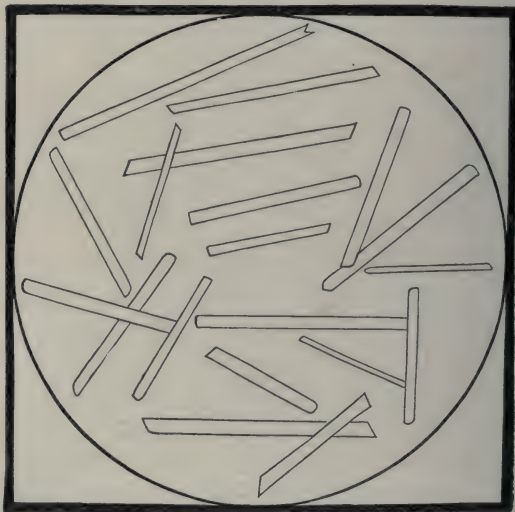


FIG. 35.

Crystals of mono-berberine sulphate (magnified 300 diameters).

when boiled with mono-sulphate of berberine, does not immediately produce a red liquid. Cold concentrated sulphuric acid dissolves it, forming at first a greenish yellow, then a brownish, and finally a dark, almost black, liquid. Hot sulphuric acid dissolves it immediately with the production of a black liquid.

Cold hydrochloric acid dissolves a small portion of mono-berberine sulphate, forming a greenish-yellow liquid, which does not change upon boiling. If hydrochloric acid, or nitric, is added to an aqueous solution of mono-berberine sulphate, a flocculent mass of crystals of hydrochlorate of berberine, or nitrate of berberine, results. These do not dissolve upon the addition of an excess of ammonia water.

Hot glacial acetic acid freely dissolves sulphate of berberine, forming an orange liquid from which, upon cooling, a mass of fine crystals separate. These are freely soluble in ammonia water, from which solution either hydrochloric acid or nitric acid produce precipitates; sulphuric acid, however, under like circumstances, forms a dark brown liquid.

Hydroxide of ammonium dissolves mono-berberine sulphate freely and immediately, sulphate of ammonium and the di-berberine sulphate resulting. If to such a solution an excess of the ordinary acids be added, combinations of these acids and berberine results, with displacement of the sulphuric acid with crystallization of the berberine salt. Advantage may be taken of this fact to prepare other salts of berberine.

Carbonate of Potassium or Sodium solutions, if dilute, freely dissolve mono-berberine sulphate. Concentrated solutions of these substances decompose it, as with hydrochlorate of berberine.

In other respects, the remarks which we have applied to hydrochlorate of berberine may be applied to this sulphate.

Solubilities.—Mono-berberine sulphate dissolves slowly in water. After agitating one part of the salt for four days with seven parts of water, it was found that 100 parts of the solution contained 1.33 parts of the salt. If a mixture of mono-berberine sulphate and water be heated, however, it rapidly dissolves, forming a supersaturated liquid, which has a dark red color, and stains glass a deep orange. It can be filtered, and sometimes permitted to remain for some days in a cool situation, without other change than the deposition of aggregations of small grainy crystals. If a little sulphuric acid be added to this supersaturated liquid (sometimes only in minute amount to a portion of it), it immediately precipitates a magma of minute crystals of mono-berberine sulphate throughout the entire liquid, and the color of the supernatant liquid changes from red to yellow.

If mono-berberine sulphate be added to a ten per cent. solution of sulphuric acid in water, until an excess of one-eighth of undissolved sulphate is present, and the mixture be heated, the sulphate will entirely dissolve, and if the solution is permitted to cool, it will form a fine magma of minute crystals. If one part of mono-berberine sulphate be quickly dissolved in twenty parts of a hot five per cent. mixture of sulphuric acid and water, and then permitted to

slowly cool, beautiful tufts of needle-like crystals result. If such a solution be digested for some hours at a temperature of 80°C , its color changes to brownish red, and upon cooling, only a small portion of the salt crystallizes. These crystals have a brown color.

Cold alcohol dissolves but a small amount of mono-berberine sulphate. After agitating one part of the salt for four days with seven parts of alcohol, the solution contained but 22 hundredths of one per cent. of the salt. Boiling alcohol, however, dissolves the salt rapidly, and in large amount, the solution being of a dark yellowish red in bulk, and orange-colored in thin layer.

Mono-berberine sulphate is insoluble in carbon disulphide, benzol, chloroform, concentrated ether, and is but slightly soluble in officinal ether.

Incompatibles.—Mono-berberine sulphate is incompatible with the mineral acids, tannic acid, gallic acid, salicylic acid, picric acid, and the soluble salts of these acids, forming precipitates when mixed with solutions of them. It is also incompatible with alkalies and the alkaline carbonates, being decomposed by these substances. Vegetable astringents usually produce precipitates with it.

DI-BERBERINE SULPHATE (NORMAL SULPHATE OF BERBERINE) $(\text{C}_{20}\text{H}_{17}\text{NO}_4)_2\text{H}_2\text{SO}_4$.—This is the most beautiful salt of berberine. It has been used in medicine for some years, but never for a sulphate. A reference to the history of the alkaloid (p. 102) will show that its discoverer was probably Prof. Procter, although previous investigators were acquainted with the soluble compound that resulted when mono-berberine sulphate was added to diluted alkaline solutions. In our paper on phosphate of berberine, we introduce testimony which demonstrates that the substance sold in commerce under the name phosphate of berberine was in reality this compound. The so-called berberine (see p. 104) made according to the ammonia process was also the di-berberine sulphate. And we can not do better than to reproduce a portion of a paper contributed by us to the American Druggist* on the subject:

“In 1878, a paper on the salts of berberine, as produced from *Hydrastis canadensis*, was presented to the American Pharmaceutical Association.† The writer announced that, when mono-berberine sulphate is added to ammonia water, by double decomposition a dark solution of berberine results, which, by mixing with alcohol, is mostly purified from the sulphate of ammonium which precipitates. . . . It is unnecessary to go over the properties of this substance in the present paper, as my object is to call attention to the fact that the substance obtained is not berberine, *but a soluble sulphate of berberine*. The writer has been aware of this fact for some years, but out of deference to an investigator who intended to consider the subject, waited for his report. However, this gentleman having withdrawn from the field, I feel at

* American Druggist, Wm. Wood & Co., Sept., 1884, p. 166.

† This was by the writer (J. U. Lloyd).

liberty to make the foregoing statement, and in addition announce the following: . . . There are two sulphates of berberine. . . . The existence of these two sulphates was announced in *New Remedies*, 1877, p. 226, by Mr. H. B. Parsons and Mr. T. J. Wrampelmeier."

Thus it is shown that the so-called berberine of our process of 1878 was in reality a di-berberine sulphate, and the equation expressing its formation is as follows: $2C_{20}H_{17}NO_4 \cdot H_2SO_4 + 2NH_4OH = (NH_4)_2SO_4 + (C_{20}H_{17}NO_4)_2H_2SO_4 + 2H_2O$. Therefore, we introduce the process we presented at that time as follows:

*Preparation of Di-berberine Sulphate.**—Rub eight parts of mono-berberine sulphate in a wedgewood mortar, cautiously adding ammonia water until in slight excess. Pour the dark liquid into thirty-two parts of boiling alcohol, and allow the mixture to stand thirty minutes, then filter. Stir into the filtrate thirty-two parts of cold concentrated sulphuric ether, and cover tightly. Surround the vessel with ice, and allow it to stand from twelve to twenty-four hours, then separate the magma of minute crystals of di-berberine sulphate with a muslin strainer or filtering paper, and dry by exposure to the atmosphere. Purify by crystallization from boiling alcohol.

Properties.—Di-berberine sulphate is an odorless, purely bitter, lemon-yellow, crystalline powder, or orange-colored crystals (it should not be red under these conditions). It crystallizes from boiling alcohol in beautiful clumps of yellow spangles, and is the finest salt of berberine known to us. (See figure 36.) When slowly crystallized in large crystals from a concentrated aqueous solution, it is garnet red. Figure 37 (next page) represents the micro-drawing made for this publication by Mr.



FIG. 36.

Crystals of di-berberine sulphate (natural size).

W. J. Huck, under the direction of Prof. F. B. Power, who describes them as follows: "These crystals are somewhat larger than those of the mono-berberine sulphate, and of an entirely different shape, several of the crystals

* In the original paper this is regarded as a process for making berberine.

frequently coalescing. As represented in the drawing (fig. 37), the crystals are magnified 60 diameters, and were mounted in Canada balsam."

Di-berberine sulphate is soluble in ten parts of water from an excess of one-eighth part of the salt, and under the same conditions in 293 parts of alcohol. When slowly added to anhydrous alcohol it dissolves, and finally a yellow magma separates, which, after being dried, is very much less soluble in water than the di-berberine sulphate, and almost insoluble in anhydrous alcohol. The chemistry of this change has not been studied, but it is not a decomposition of the di-berberine sulphate, with the formation of a molecule each of berberine and mono-berberine sulphate, as might be possible, for, $(C_{20}H_{17}NO_4)_2 \cdot H_2SO_4 = C_{20}H_{17}NO_4 + C_{20}H_{17}NO_4 \cdot H_2SO_4$. In one instance a specimen of several ounces of crystallized di-berberine sulphate, that had been kept in a securely sealed vial for three years, became altered in properties, and almost insoluble in water.

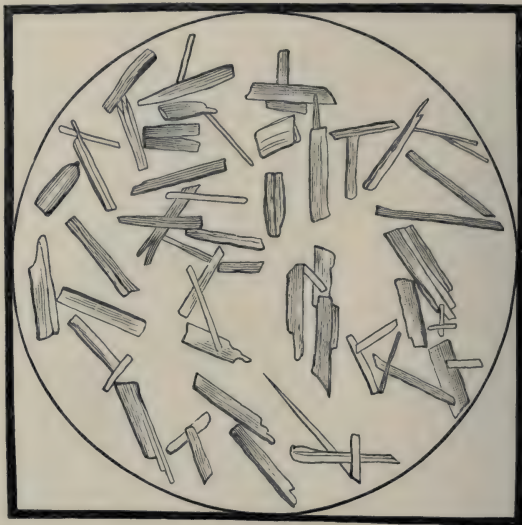


FIG. 37.

Crystals of di-berberine sulphate (magnified 60 diameters).

PHOSPHATE OF BERBERINE ($C_{20}H_{17}NO_4 \cdot 7H_4PO_4 + 4H_2O$).—A substance was introduced into commerce by Dr. T. L. A. Greve, about the year 1877, under this name, and supposed to be a phosphate of berberine. It was in order to meet the demand for a more soluble salt than either the muriate or mono-berberine sulphate, which at that time were the only salts of berberine used in American medicine. This substance was made by Dr. Greve* by digesting in boiling water a mixture of mono-sulphate of berberine, and precipitated phosphate of calcium, filtering, evaporating the filtrate to dryness, dissolving the residue in boiling alcohol to free it from sulphate of calcium, and evaporating the filtered alcoholic solution to dryness.†

In 1877, Prof. H. B. Parsons presented to the Michigan Pharmaceutical Association a process for making phosphate of berberine, and in connection with Mr. T. J. Wrampelmeier, followed it in *New Remedies*, 1878, p. 226, by an interesting paper on the subject.

They prepared a salt in accordance with the process of Dr. Greve, but found from an analysis that it was free from phosphoric acid, the "*faint trace*" present existing as an impurity in the form of bone ash. Subsequent

* Eclectic Medical Journal, Cincinnati, 1877, p. 311.

† Dr. Greve states that, "The above process may also be varied by substituting phosphate of lead, or phosphate of barium, for the lime salt."

analyses demonstrated that the salt was a sulphate of the composition $(C_{20}H_{17}NO_4)_2 \cdot H_2SO_4$.*

Messrs. Parsons and Wrampelmeier then made the soluble calcium ortho-phosphate. An excess of this acid calcium phosphate, $CaH_4(PO_4)_2$, was then treated with mono-sulphate of berberine, when a precipitate of calcium sulphate resulted. The mixture was then evaporated nearly to dryness, and treated with hot diluted alcohol, whereby the remainder of the calcium salts were precipitated. The hot alcoholic solution of a berberine salt was then separated, by filtration, from the insoluble calcium salts, evaporated nearly to dryness, and then mixed with cold alcohol. A canary-yellow precipitate resulted, which, upon examination, proved to be a phosphate of berberine.

Phosphate of berberine was then made by Mr. Wrampelmeier, the acid phosphate of barium, $BaH_4(PO_4)_2$, being used instead of the ortho-calcium salt. This product agreed in every respect with that obtained by the other experiment.

Analysis and Properties.—Phosphate of berberine exhibited a strong affinity for water, a long exposure, at from 67° to 70° C, being required to free it from moisture. The mean of two experiments, after the salt ceased to lose weight by an exposure of 100° C, resulted as follows :

.2803 gram lost .0181 gram = 6.45 per cent.
 .3034 gram lost .0200 gram = 6.59 per cent.
 Average loss at 100° C, 6.52 per cent.

After destroying the organic matter by means of sulphuric and nitric acids, the phosphoric acid was estimated according to Fresenius' method, as magnesium pyrophosphate.

.3034 gram gave .2145 gram $Mg_2P_2O_7$ = 1894 of H_3PO_4 .
 .2803 gram gave .2000 gram $Mg_2P_2O_7$ = 1766 of H_3PO_4 .

The average being 62.67 % of the phosphate of berberine employed.

The berberine was estimated by means of platinic chloride. According to Perrins, the precipitate has the formula $2C_{20}H_{17}NO_4 \cdot 2HCl \cdot PtCl_4$. Of which 18.22 % is platinum, and 61.899 % is berberine.

Phosphate of Berberine.	Precipitate.	Berberine.	Berberine estimated from platinum in ash.	Berberine.
.2517 gram gave	.1312 gram =	.0812.	.0815.	32.37 per cent.
.1727 gram gave	.0900 gram =	.0557.	.0526.	30.45 per cent.
.1224 gram gave	.0640 gram =	.0396.	.0390.	31.86 per cent.

The platinum in the precipitates was then estimated from the ash, and the berberine calculated, which was considered more reliable than the preceding process, as it excluded a source of error in the tared filter paper. The result is shown in the last two columns of the above table. The average of berberine from the platinum of the ash being 31.56 %.

* Dr. Greve, therefore, struck upon the soluble di-berberine sulphate, which the writer also obtained, about the same time, by another process. Neither of us assigned it to its proper position.

SUMMARY OF THE ANALYSIS.

	Percentage Found.	Percentage Calculated.
Water (H ₂ O)	6.52	6.58 per cent.
Phosphoric Acid (H ₃ PO ₄)	62.67	62.76 per cent.
Berberine (C ₂₀ H ₁₇ NO ₄)	31.56	30.65 per cent.
	<u>100.75</u>	<u>99.99 per cent.</u>

These results give C₂₀H₁₇NO₄·7H₃PO₄+4H₂O, as the formula for phosphate of berberine.* The following equation expresses the reactions: C₂₀H₁₇NO₄·H₂SO₄+6[BaH₄(PO₄)₂]=C₂₀H₁₇NO₄·7H₃PO₄+BaSO₄+5BaHPO₄.

This being the only analysis of a compound of phosphoric acid and berberine known to us, we deemed it desirable to add further information to this subject. Accordingly, we brought the matter to the attention of Prof. Virgil Coblentz, who agreed to make an ultimate analysis of the compound, and in this connection we call attention to the fact that the salt was made by him by the direct combination of phosphoric acid and crystallized berberine, instead of by double decomposition. We therefore introduce the following report: †

Preparation.—(Contributed to this publication by Prof. Virgil Coblentz). An accurately weighed quantity of the pure alkaloid, prepared by Prof. J. U. Lloyd, was dissolved in a sufficient amount of absolute alcohol, and into this solution exactly two grams of phosphoric acid (H₃PO₄) was weighed, the strength of which had been previously ascertained, two grams containing 1.2421 grams of absolute H₃PO₄. Then an equal bulk of absolute ether was added, and after allowing sufficient time for complete separation the mixture was thrown on a filter paper and the precipitate thoroughly washed with a mixture of alcohol and ether. The filter and contents were then removed and boiled in an excess of alcohol to remove all traces of adhering free acid, cooled, and mixed with its bulk of ether. The precipitate that formed was again thrown on a new filter and washed with a mixture of alcohol and ether until it was found to be free from uncombined phosphoric acid.

Gravimetric Estimation.—An amount of the alkaloid berberine weighing 0.460 grams was dissolved in absolute alcohol and treated as we have described. The liquids and washings were mixed and distilled water added; the ether and alcohol then evaporated by a gentle heat. To this aqueous solution of the free acid, ammonia water in slight excess was added and subsequently test magnesium mixture, until after having been well stirred and permitted to stand, no further precipitate followed the addition of the reagent. Ammonia water equal to one-fourth the volume of the liquid was then added, the vessel covered and allowed to stand for twelve hours. The precipitate of ammonio-

* "This formula seems, at first sight, an improbable one; but any person who will take the pains to look up the formulæ for the phosphates of the other alkaloids, will be surprised at their lack of uniformity, and at the fact that alkaloids exhibit no particular quantivalence."—PARSONS and WRAMPFELMEIER.

† Prof. F. B. Power is also estimating the composition of phosphate of berberine, using a salt made by us, and crystallized from alcohol. Unfortunately, his report is not ready, and we will, therefore, present it to our readers at a future day in the Addenda.

magnesium phosphate was then collected on a filter and washed with a solution consisting of one part of officinal ammonia water and three parts of water, until the washings no longer produced a turbidity in a solution of nitrate of silver acidulated with nitric acid. The precipitate was then dried at $100^{\circ}\text{C}.$, and ignited in a weighed crucible to low redness. From the weight of the resulting magnesium pyrophosphate ($\text{Mg}_2\text{P}_2\text{O}_7$), the amount of phosphoric acid contained in the solution was calculated, 100 parts of $\text{Mg}_2\text{P}_2\text{O}_7$ corresponding to 88.39 parts of H_3PO_4 . 0.3297 grams of magnesium pyrophosphate were obtained from the solution, which corresponds to 0.2915 grams of phosphoric acid. Therefore, if from the 1.2421 grams of anhydrous H_3PO_4 contained in two grams of the phosphoric acid used we deduct the 0.2915 grams that remained uncombined, we have 0.9506 grams in combination with the berberine.

If one molecule of berberine $\text{C}_{20}\text{H}_{17}\text{NO}_4$ (335), combined with one molecule of H_3PO_4 (99), 0.460 grams of berberine would require 0.13595 grams of phosphoric acid. In reality nearly 0.9513 grams of acid are required theoretically to represent seven molecules of phosphoric acid, as $(.9513 \div .13595)$; this number corresponds closely to that actually found, 0.9506.

Four estimations were made in accordance with the foregoing scheme, resulting as follows:

No. 1 gave 0.9506 grams of phosphoric acid (H_3PO_4), from 0.460 grams of phosphate of berberine.

No. 2 gave 0.9509 grams of phosphoric acid (H_3PO_4), from 0.460 grams of phosphate of berberine.

No. 3 gave 0.9508 grams of phosphoric acid (H_3PO_4), from 0.460 grams of phosphate of berberine.

No. 4. gave 0.9509 grams of phosphoric acid (H_3PO_4), from 0.460 grams of phosphate of berberine.

The average, 0.9508, is practically close enough to the theoretical amount, 0.9513, to show that one molecule of berberine phosphate must contain seven molecules of phosphoric acid, therefore making the formula $\text{C}_{20}\text{H}_{17}\text{NO}_4 \cdot 7\text{H}_3\text{PO}_4$.

Volumetric Estimation.—This method depends on the indirect process of neutralization. 0.280 grams of the berberine were dissolved in absolute alcohol and phosphate of berberine was made as detailed on p. 124. The filtered mixture of alcohol and ether, containing the uncombined phosphoric acid, was then mixed with distilled water, and the ether and alcohol evaporated by a gentle heat. Into the aqueous solution that remained a normal solution of hydroxide of sodium was allowed to flow until sufficient of the latter was employed to insure the formation of the neutral sodium salt Na_3PO_4 . Solution of chloride of barium was then added to this strongly alkaline liquid until no further precipitate was produced. After some hours, the resulting $\text{Ba}_3(\text{PO}_4)_2$ was collected on a filter and well washed with water, the filtrate and washings being collected in a beaker. This was colored with solution of

litmus and a normal solution of sulphuric acid was allowed to flow into it from a burette until a permanent pink hue resulted. The number of C. c. of normal acid solution required, deducted from the number of C. c. of the alkaline solution, was accepted as giving the amount of the latter required for the exact neutralization of the phosphoric acid; one C. c. of the normal alkali corresponding to 0.327 grams of anhydrous phosphoric acid.

SUMMARY OF THIS EXPERIMENT.

1.2421 grams of H_3PO_4 were contained in the 2 grams of acid used.
0.6638 " " " remained uncombined.

0.5783 " " " combined with the 0.280 grams berberine.

42.3 C. c. of normal solution NaOH used to neutralize the free acid.
22.0 " " " H_2SO_4 " " excess of NaOH.

20.3 C. c. amount required for exact neutralization of uncombined H_3PO_4 .
Hence, 20.3 C. c. $\times .0327 = 0.6638$ grams of H_3PO_4 uncombined.

Four more experiments were made with the following result :

Experiment.

No. 1.	0.280	grams	berberine	$\text{C}_{20}\text{H}_{17}\text{NO}_4$	yielded of H_3PO_4	0.5790	grams.
No. 2.	0.280	"	"	"	"	0.5788	"
No. 3.	0.280	"	"	"	"	0.5787	"
No. 4.	0.280	"	"	"	"	0.5788	"

If one molecule $\text{C}_{20}\text{H}_{17}\text{NO}_4$ (335) combines with one molecule of H_3PO_4 (99), then 0.280 gram alkaloid would require 0.827, but we find practically that 0.280 gram of the alkaloid combines with on an average 0.5788 gram of the acid. Then, as $0.5788 \div 0.0827$ equals about seven, hence if theoretically 0.5792 gram of the acid combine with .280 gram of the alkaloid, and practically the amount found is about 0.5788 of acid, the formula must then be $\text{C}_{20}\text{H}_{17}\text{NO}_4 \cdot 7\text{H}_3\text{PO}_4$.

Properties.—Phosphate of berberine is a canary yellow powder, odorless and bitter. It changes to olive green when heated above 70°C ., and gives up its water of crystallization at 100°C . It absorbs water upon exposure, and changes to a darker yellow, but does not deliquesce. Crystallized from hot alcohol, it forms irregular prismatic crystals. (P. and W.)

The crystalline structure of phosphate of berberine is represented by the micro-drawings (Fig. 38) made for our publication by Mr. W. J. Huck, under the direction of Prof. F. B. Power, who writes of them as follows: "The crystals are much broader than those of the preceding salts in consequence of the coalescence of several crystals, and the ends are very irregular in outline."

Solubilities.—One part of the crystallized salt dissolved in 10.43 parts of cold water.

One part of the salt dried at a temperature of 100°C . dissolved in 21.52

parts of cold water. It is almost insoluble in cold alcohol, and insoluble in pure alcohol, ether, and chloroform.

There is really no preference to be made for the pure phosphate over the di-berberine sulphate, which was really introduced for a phosphate. This fact has necessitated a longer paper than would be demanded by the phosphate in such a work as ours.

NITRATE OF BERBERINE.

$C_{20}H_{17}NO_4 \cdot HNO_3 + H_2O$ (Perrins).

—Nitrate of berberine is sometimes used in medicine, but not as extensively as the muriate.

Preparation.—Nitrate of berberine is to be made according to the process employed in making the hydrochlorate, except that nitric acid is used instead of hydrochloric. This process can be followed even to the washing of the salt, for it is but slightly soluble in cold water. It should be dried, however, by exposure to a cool atmosphere, because decomposition follows when it is heated, especially if slightly moist.

Properties.—Nitrate of berberine obtained in this manner is in the form of a lemon yellow crystalline powder, odorless when fresh. It slowly dissolves in the mouth, imparting a bitterness to the taste. When kept for any length of time, especially during warm weather, or when heated in a test tube, it decomposes, evolving NO, and changes to a reddish color. The ultimate effect of this decomposition upon the constitution and properties of the residue has never been determined. According to Perrins it is perfectly stable at $100^\circ C.$, but we have known it to decompose and evolve NO when kept in bulk at the ordinary temperature and become unfit for use. We do not consider it a desirable compound.

When nitrate of berberine is added to cold nitric acid, a dark brownish-red solution results, which, upon warming, changes to orange-red, with the evolution of an abundance of nitric oxide (NO). If one part of nitrate of berberine is gradually added to eight parts of hot nitric acid, nitric oxide is rapidly evolved, and finally the liquid changes from brown to a ruby red color. This solution has the characteristics which we have described (p. 113), under "Nitric Acid, Action on Hydrochlorate of Berberine," dissolving in the same solvents and contra, forming a yellow precipitate with water, and otherwise reacting so as to indicate that the products of decomposition in both cases are perhaps identical. Less heat, however, is required to produce the re-

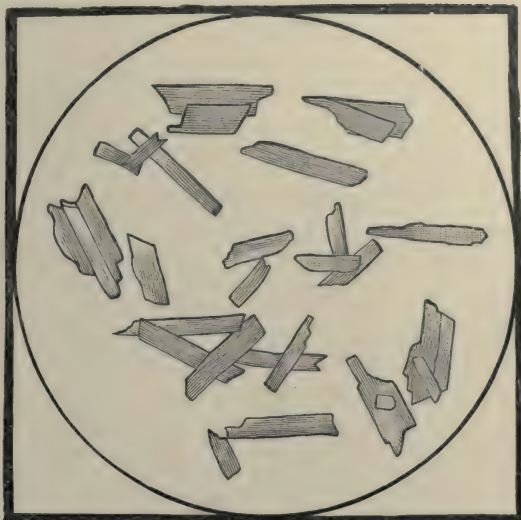


FIG. 38.

Crystals of phosphate of berberine (magnified 300 diameters).

action between nitrate of berberine and nitric acid than between hydrochlorate of berberine and nitric acid.

Nitrate of berberine dissolves in cold sulphuric acid, forming a dark brown or black liquid, which does not change upon heating. Dilute sulphuric acid (1 to 7) forms a red liquid if boiled with nitrate of berberine. This color is not affected by an excess of hydrochloric acid, but is changed to brown by an excess of ammonia water. Nitrate of berberine dissolves slightly in cold hydrochloric acid. If a mixture of nitrate of berberine and hydrochloric acid be boiled, the salt is decomposed, a dark brown liquid resulting.

Hot glacial acetic acid freely dissolves nitrate of berberine with the production of a dark orange-colored liquid, which, upon cooling, deposits an abundance of yellow crystals. These dissolve freely in ammonia water, and from this solution hydrochloric acid precipitates masses of hydrochlorate of berberine. Under the same circumstances either sulphuric or nitric acid, with the aforementioned ammoniacal solution, forms a deep red liquid.

Nitrate of berberine will dissolve to an extent in cold ammonia water and more freely upon boiling, and crystallizes from the latter solution upon cooling. It corresponds with hydrochlorate of berberine in its deportment towards dilute or concentrated solutions of the hydroxides of potassium or sodium.

Nitrate of berberine is insoluble in benzol, carbon disulphide and concentrated sulphuric ether. It is slightly soluble in alcohol, and more so in water.

The saturated solution of nitrate of berberine in cold water has a greenish yellow color. From this solution most of the berberine in the form of crystalline salts is deposited by nitric, sulphuric or hydrochloric acid, but not by the addition of acetic or phosphoric ($H_3 PO_4$), acid. No precipitate follows when magnesium sulphate, ammonium oxalate, lead acetate or copper sulphate are added to the aqueous solution, but a precipitate follows with potassium ferrocyanide (greenish), potassium chromate and potassium bichromate (yellow), and potassium iodide (yellow and gelatinous). Picric acid, picrate of ammonium, and solutions of the soluble picrates precipitate berberine completely from the solution of nitrate of berberine, the result being picrate of berberine.

CITRATE OF BERBERINE—Preparation.—This may be made by direct combination between solution of citric acid and berberine. When a solution of one part of di-berberine sulphate is dissolved in sixteen parts of water and two parts of citric acid are added, and the solution permitted to stand for some days in a cool location, beautiful tufts of crystals are formed. These are of a fibrous, silky texture, very bitter, permanent, and are free from sulphuric acid. (Figure 39), next page. They have never been analyzed. Citrate of berberine is not very soluble in cold alcohol or water, but more freely in boiling.

A cold aqueous solution of citrate of berberine has a greenish yellow color. Either sulphuric, hydrochloric, or nitric acid produces precipi-

tates when added to this liquid. Citrate of berberine is not precipitated from aqueous solution by solution of magnesium sulphate, ammonium oxalate or copper sulphate. Precipitates result, however, from the addition of potassium iodide (gelatinous), potassium ferrocyanide, potassium chromate, potassium bi-chromate and by acetate of lead. This last (acetate of lead), differs from the reaction with nitrate of berberine. Picric acid or picrate of ammonium precipitates the berberine completely.

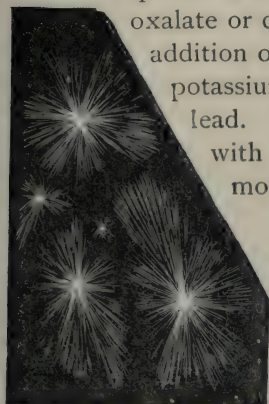


FIG. 39.
Crystals of citrate of berberine,
(natural size).

Citrate of berberine corresponds with nitrate of berberine and sulphate of berberine in its deportment towards concentrated sulphuric acid. If boiled with an excess of dilute sulphuric acid (1 to 7), the solution acquires a slight brownish tint and does not change by the addition of either hydrochloric acid or ammonia water.

Hydrochloric acid dissolves citrate of berberine to a slight extent, forming a yellow liquid, which is not changed by boiling.

Citrate of berberine corresponds with nitrate of berberine in its deportment towards glacial acetic acid and nitric acid.

Solubilities.—Citrate of berberine is insoluble in benzol, carbon disulphide, concentrated ether, and chloroform. It is slightly soluble in officinal ether.

Ammonia water is a good solvent for citrate of berberine, a reddish-brown liquid resulting.

PICRATE OF BERBERINE.—This substance is formed when picric acid, or a soluble picrate, is added to the solution of any other salt of berberine. This compound is not used in medicine outside of the Homœopathic school, but it is of considerable interest to us as a test for berberine. We shall refer more fully to the characteristics of picrate of berberine hereafter.

Boiling distilled water dissolves very small portions of picrate of berberine, and upon cooling the solution, the salt separates entirely in crystalline form.

Picrate of berberine is insoluble in cold water, alcohol, ether, chloroform, benzol or carbon disulphide.

Nitric acid reacts with picrate of berberine in a manner similar to the action of that acid and hydrochlorate of berberine. The liquid which results from the action of hot nitric acid on picrate of berberine differs from that produced by hydrochlorate of berberine, as follows: With sulphuric acid it forms a red solution, which becomes lighter colored and cloudy on standing. It mixes with water in all proportions, forming clear solutions.

Sulphuric acid, hydrochloric acid and glacial acetic acid react with picrate of berberine similar to the manner in which they do with hydrochlorate of berberine.

Hydroxides of ammonium, sodium or potassium react as follows: Cold

dilute solutions scarcely affect it, and boiling dilute solutions dissolve it very sparingly. Concentrated solutions of these alkalies dissolve it more freely, and if these solutions are rendered acid with sulphuric acid, a cloudiness results, which is dissipated by the addition of ammonia water.

Picric acid and the soluble picrates completely separate berberine and berberine salts from aqueous solution.

DETECTION AND ESTIMATION OF BERBERINE.—In the first natural order of plants, we have yet to consider two that contain berberine. These are *Coptis trifolia* and *Xanthorrhiza apiifolia*, and we shall introduce the processes for estimating the alkaloid when we reach the latter plant.

HYDRASTINE (THE WHITE ALKALOID OF *HYDRASTIS CANADENSIS*). $C_{22}H_{23}NO_6$ —*History of Hydrastine*.—In April, 1851, Mr. Alfred B. Durand published an essay in the American Journal of Pharmacy on *Hydrastis canadensis*. He had obtained, among other substances, a crystallizable body, and was inclined to view it as an alkaloid. With the light now before us, we know that his supposition was true, but in view of the fact that he could not make a crystallizable salt, he left the matter open, as follows: “For the present I shall therefore call the substance *Hydrastine*, with the hope that I will be more successful, after repeating my experiments on a large scale, in fully establishing its rank among the alkaloids.” Since the alkaloid has not, as yet, yielded crystallizable salts with the acids Mr. Durand combined with it, viz. : nitric, hydrochloric, acetic and oxalic, it is not strange that he failed to obtain crystals. It seems that he neglected to continue his work ; at least, he published nothing further on the subject. Hence, while the honor of the discovery belongs to Mr. Durand, the investigation of the character of the alkaloid and its salts must be placed to the credit of subsequent investigators ; and in view of the opinions held by some persons, who believe that other parties discovered the alkaloid, we introduce a condensation of Mr. Durand’s original process :

The crushed root of *Hydrastis canadensis* was macerated with cold water and then percolated with that menstruum, the percolate afterward being evaporated to dryness. 500 grains of the residue was dissolved in eight ounces of water, 125 grains of oxide of magnesium added, and the mixture digested on a sand bath for two hours, and then filtered. The residue within the filter paper was dried, digested in boiling alcohol, filtered, and the filtrate allowed to evaporate spontaneously. The result was, to use Mr. Durand’s words, “beautiful, brilliant, yellow, four-sided, prismatic crystals, terminated by pyramidal summits.”

In reviewing the process of Mr. Durand, it will be seen that, when the aqueous liquid obtained from the root was digested with magnesia, the acid then in natural combination with the white alkaloid united with the magnesia. This reaction was followed by precipitation of that alkaloid, which is insoluble in water, thus producing the “residue.” This residue, upon being dried, was exhausted with boiling alcohol, in which menstruum, the alkaloid, is very soluble, and from it hydrastine was obtained in colored crystals by spontaneous

evaporation of the alcohol. In describing these crystals, Mr. Durand identified the white alkaloid of hydrastis so clearly as to leave no doubt in the mind of any person familiar with the alkaloids of hydrastis. He states "it is insoluble in water, sparingly so in cold ether and alcohol, more so in ether when hot, entirely dissolved by chloroform and boiling alcohol."

The white alkaloid, hydrastine, is the only product of hydrastis that will conform to the foregoing description.

The color of Mr. Durand's alkaloid, a "brilliant yellow," was due to the presence of berberine, for that substance is most tenaciously held by hydrastine, and many re-crystallizations are necessary before it can be obtained colorless. (See preparation of hydrastine, p. 132, and Hale's "third alkaloid," p. 140).

Nothing was then written on the subject of hydrastine for a period of eleven years, although Prof. E. S. Wayne, of Cincinnati, made and presented to Prof. Procter (1856) a sample that, to use the words of Prof. Procter in the American Journal of Pharmacy, July, 1862, was "Identical in appearance and character with Durand's, except that it was lighter in color."

The next paper appeared in the American Journal of Pharmacy, July, 1862. The author, Mr. Wm. S. Merrell, speaks of having recently discovered two alkaloids in the rhizome of *Hydrastis canadensis*, and he proposed for them the names hydrastia and hydrastina. Both of these alkaloids had been discovered previously, one (hydrastia) being the well-known berberine. His description of that for which he proposed the name hydrastina, identified it as the alkaloid discovered in 1850,* by Durand, and prepared in 1856 by Wayne. Mr. Merrell's proposed name could not, therefore, be accepted, and as the sample Mr. Merrell submitted to the editor of the Journal of Pharmacy was darker in color than either that made by Mr. Durand or Prof. Wayne, nothing was added to the literature on this subject.

The alkaloid had not yet been purified, all the parties reporting that it was either yellow (Durand and Wayne) or greenish (Merrell). The production of the pure alkaloid was reserved for Mr. J. Dyson Perrins, who announced it in the London Pharmaceutical Journal, May, 1862. He purified it by repeated crystallizations from hot alcohol, and described it as crystallizing in "four-sided prisms, and of great brilliancy," and he said of it, "the crystals are white."

Mr. F. Mahla, of Chicago, next contributed to the American Journal of Science and Arts, July, 1863, a paper on this alkaloid, and in 1878, the writer (J. U. Lloyd), read a paper before the American Pharmaceutical Association, on its preparation.

This brings us to the present year, and to the most important paper that has been written on the subject. It was by Prof. Frederick B. Power, of the University of Wisconsin, and was contributed to the American Pharmaceutical

* Mr. Durand's paper was written in the summer of 1850, and published in 1851.

Association, 1884, and we shall make many references to this admirable treatise.

Preparation.—Hydrastine has always been made by decomposing the natural salt by means of an alkali. We introduce the process contributed by us to Prof. Power, by which we prepared the alkaloid examined by that gentleman, it is as follows:

“One thousand pounds of powdered *Hydrastis canadensis* were properly moistened with alcohol, packed in a suitable percolator, and percolation then conducted with the use of officinal alcohol as a menstruum. Sulphuric acid, in strong excess, was added to the percolate, and, after four hours, the supernatant liquid was filtered from the mass of crystals of sulphate of berberine ($C_{20}H_{17}NO_4 \cdot H_2SO_4$). To this filtrate ammonia water was added until it showed but a slightly acid reaction, then strained to separate the precipitated sulphate of ammonium, distilled to a syrupy consistence, and the residue poured into ten times its bulk of cold water. After twenty-four hours the precipitated resinous substances, oils, etc., were separated from the liquid by filtration, the filtrate being an impure solution of sulphate of hydrastine. Ammonia water, in decided excess, was then added to this resultant liquid, and the precipitate of impure hydrastine collected and dried. It was then digested with one hundred times its weight of cold water, to which sulphuric acid was carefully added to *slight* acid reaction, and, after twenty-four hours, filtered. The filtrate was again precipitated with excess of ammonia water, the precipitate collected on a strainer and dried. This precipitate was powdered and extracted with boiling alcohol, from which impure, dark yellow crystals of hydrastine separated when the alcoholic solution was cooled. The crystals were purified by repeated crystallizations from boiling alcohol. In order to obtain the hydrastine perfectly colorless, when in the form of large crystals, many crystallizations are necessary.”

Where the operator labors under the disadvantages of imperfect apparatus, thus entailing a great loss of alcohol, water can be used as a menstruum. However, under these circumstances, impurities are introduced that are not present when alcohol is used. The mother liquor from berberine sulphate

(see page 117) can be used and adapted to this process.

Crystalline Form and Appearances.—Hydrastine always forms imperfect crystals. Even when slowly crystallized, in large quantity, they are irregularly developed, and as they almost invariably form in such a way as to present their lateral surfaces to the solution, it is difficult to obtain good specimens. Figure 40 illus-

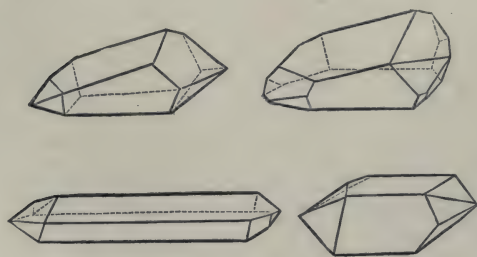


FIG. 40.
Crystals of Hydrastine (natural size).

trates a few crystals that were selected from a batch of eight pounds of the alkaloid, and present the most perfect of the specimens, and as they appeared in the solution. They are such as Prof. Power employed in making his measurements. The following description is that of Prof. Power, and figures 41 and 42 represent the perfected crystals as constructed by that gentleman.

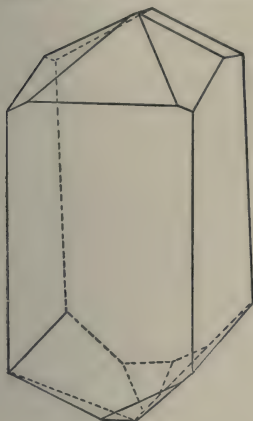


FIG. 41.

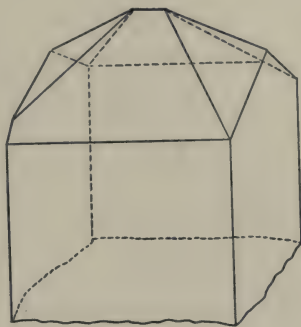


FIG. 42.

Crystals of Hydrastine (enlarged and perfected by Prof. F. B. Power).

"The crystals, which attain a maximum length of from eight to ten millimeters, have the form of four-sided prisms (Fig. 41 and 42), and apparently belong to the ortho-rhombic system, although the goniometer at my disposal did not admit of the exact measurement of the angles. The drawings here presented, which represent typical crystals, were formed by making an orthographic projection, and the angles may be said to be as geometrically accurate as is possible to obtain them without absolute measurements.* In Fig. 42 the terminal faces are shown to be very perfectly developed, while Fig. 41 represents a crystal as viewed somewhat from the side and from above, the terminal faces not so symmetrically developed, and therefore having a somewhat more complicated form. It is interesting to observe that when both ends of the crystals are developed, as shown in Fig. 41, the corresponding terminal faces of opposite ends are invariably inclined to each other at an angle of exactly 90° ."

Hydrastine can be crystallized in glassy crystals, perfectly colorless and very brilliant. As a rule, however, the crystals are opaque and white, owing to the presence of numerous fractures. When in this form and in small crystals, it may be quite colored and appear white.

Chemistry of Hydrastine.—The first analysis was made by Mr. F. Mahla,* who assigned to it the composition $C_{22}H_{24}NO_6$. From his figures Kraut deduced the formula $C_{22}H_{23}NO_6$ †. Thus it is that the investigation of Prof. Power, in 1884, is the second published contribution to the subject, although Prof. J. F. Eykman, of Tokio, Japan, has investigated the subject, but has not, as yet, published the results of his analysis.‡ Prof. Power's analysis coincided very nearly with that of Mr. Mahla, although he followed a different method for making his determination. The following table compares the results of the analyses:

* Silliman's American Journal, Vol. 36, No. CVI., p. 57.

† See Power's paper on Hydrastine, Proceedings of the American Pharmaceutical Association, 1884.

‡ We are informed by Prof. Eykman that he is especially interested in the decomposition products of this alkaloid, and we hope some day to present his paper.

Calculated for $C_{22}H_{23}NO_8$	Prof. Power found.	Mr. Mahla found.	
C=66.48 per cent.	66.69 per cent.	66.69	66.38
H= 5.79 per cent.	5.61 per cent.	6.01	5.69
N= 3.53 per cent.	3.46 per cent.	3.83	3.76
O=24.20 per cent.			
100.			

Prof. Power states that "The results of both our analyses are seen to agree quite closely with the accepted formula, which may, therefore, now be presumed to be correct.

Properties of Hydrastine.—Hydrastine unites with the acids, and forms salts, none of which have as yet been crystallized. Prof. Power failed to produce a crystal, and we have exposed large amounts of the muriate, sulphate and citrate, to the most favorable conditions, and to a temperature of -28° C. in lots of ten pounds, without success. By spontaneous evaporation a glassy substance invariably remains, destitute of crystalline form.

When a salt of hydrastine is dissolved in water and then precipitated by an alkali, the result is a bulky amorphous magma of the alkaloid. This begins to shrink in bulk in a short time, and finally assumes a crystalline form, when the product will occupy but a small proportion of the bulk of the original magma. The addition of alcohol to such a precipitate hastens the change from the amorphous to the crystalline. Impure hydrastine precipitates white, owing to the minute division, but becomes very dark after assuming the crystalline form, carrying the coloring matters with it. For this reason it is not practical to purify the alkaloid by repeated solutions in acid water and precipitations with an alkali. Although mono-berberine sulphate is quite soluble in dilute ammonia water (forming the di-berberine sulphate), and hydrastine is perfectly insoluble in that menstruum, it is impossible to separate the berberine from sulphate of hydrastine by the method of precipitation. The tenacity with which the hydrastine holds this yellow alkaloid under these conditions led the writer to doubt for a long time the identity of this yellow substance and berberine (and others have been misled); but by repeated crystallizations of impure (yellow) hydrastine from boiling alcohol, a deep yellow liquid was obtained that, upon purification, yielded a considerable amount of berberine. One experiment, wherein a batch of six and one-half pounds of impure hydrastine was worked, yielded three and one-half ounces of mono-sulphate of berberine. (See Hale's "Third Alkaloid," p. 142.)

Hydrastine is tasteless if the saliva is of alkaline reaction. Its soluble salts are acrid.

Action of Reagents on Hydrastine.—According to Prof. Power, "The crystals of hydrastine are affected in the following manner by reagents:

"Concentrated sulphuric acid produces a yellow color, which, in contact with a crystal of potassium bichromate, becomes brown. Concentrated sulphuric acid, on warming, produces a bright red color. Concentrated nitric acid produces, in the cold, a yellow color, changing to reddish-yellow. Con-

centrated hydrochloric acid gives no coloration, either in the cold or upon warming. Concentrated sulphuric acid and monohydrate of ammonium gives an olive-green color, which appears to be its most characteristic test."

The solution of the hydrochlorate is affected as follows by reagents (Power):

"Ammonia water and the fixed alkalies give a white, curdy precipitate, sparingly soluble in excess; potassium iodide, potassium-mercurio iodide, potassium ferrocyanide, potassium sulphocyanide, mercuric chloride and tannic acid produce white precipitates; iodine and potassium iodide, a light brown precipitate; potassium bichromate, a yellow precipitate; picric acid, a bright yellow precipitate; platanic chloride, an orange yellow precipitate; auric chloride, a deep yellowish-red precipitate."

Decomposition Products of Hydrastine.—Crystals of hydrastine fuse "at 132° C. (Mahla states 135° C.), to a light amber-colored liquid. When heated on platinum-foil they decompose with the evolution of empyreumatic, inflammable vapors, reminding, as Mahla had previously observed, somewhat of carbolic acid, and leaving a large amount of ash, which burns slowly away at a red heat. In order to ascertain whether hydrastine is capable of yielding a hydro compound, five grams of the alkaloid were dissolved in dilute sulphuric acid, and subjected for about two days to the action of nascent hydrogen, as developed from metallic zinc and platinum. The liquid was then filtered, precipitated by ammonia water, in slight excess, and the precipitate, after washing, dissolved in hot alcohol, and allowed to crystallize. The crystals are insoluble in water, and closely resemble in appearance those of hydrastine, but possess a slightly yellowish tint, which could not be removed by repeated crystallization. The melting point also lies close to that of hydrastine, being observed at 131° C. I have not as yet subjected these crystals to ultimate analysis, but have formed therefrom and analyzed the hydrochlorate. The latter, like the hydrochlorate of hydrastine, is amorphous, and remains, by the evaporation of its solution, in the form of a transparent, yellowish varnish, yielding, however, a nearly white powder, freely soluble in water. After drying at 100° C., 0.7830 gram of substance gave 0.2560 gram AgCl = 0.0651 gram HCl , or 8.31 %.

"This result would therefore indicate that a *hydro-hydrastine* is thereby formed, by the absorption of four atoms of hydrogen, and is analogous in composition to hydroberberine, $\text{C}_{20}\text{H}_{21}\text{NO}_4$ (Ann. Chem. Pharm. Suppl., 2, 191).

Calculated for $\text{C}_{22}\text{H}_{17}\text{NO}_6 \text{HCl}$.	Found.
HCl = 8.34 per cent.	8.31 per cent."

—Power.

Prof. Power also formed combinations of hydrastine and both bromine or iodine, such reactions being accompanied by the evolution of considerable

heat, but he did not determine the composition of such compounds. By distilling a mixture of the alkaloid and caustic potash, unpleasant, inflammable vapors escaped, and a yellowish brown mass remained. Upon dissolving this in water and adding sulphuric acid until in slight excess, and distilling the liquid, formic acid was detected in the distillate. The residual acid liquid upon agitation with ether, and evaporation of the ethereal solution, yielded protocatechuic acid ($C_7H_6O_4$); and no other acids were identified. (This acid is also obtained as a decomposition product of berberine; see p. 109).

Upon treating hydrastine in alcoholic solution with ethyl iodide and subjecting it to heat, hydriodic acid was evolved, and the reddish yellow syrup that remained upon dilution with alcohol deposited a white crystalline powder. This dissolved freely in warm water, and crystallized colorless upon cooling. These were anhydrous, fused at about $183^\circ C.$, but underwent decomposition by the application of heat. An analysis of this substance demonstrated that it had the composition $C_{22}H_{22}$ (C_2H_5), NO_6HI , and was evidently the *hydriodate of ethyl-hydrastine*. Since this compound was formed by the substitution of the ethyl radical (C_2H_5), for one atom of hydrogen of the molecule of hydrastine, Prof. Power considers hydrastine to be a secondary or imide base, and he writes as follows:

"In this respect, according to Henry* and Bernheimer,† it occupies an analogous position to berberine, since they obtained from the latter mono-ethyl and methyl derivatives, while, according to Perrins and Schmidt, in the case of berberine, the simple hydriodate of the base is thereby formed.

"That the crystalline compound obtained from hydrastine is really an ethyl derivate is evident, not only from the analysis, but I have also prepared the simple hydriodate by dissolving the alkaloid in freshly prepared hydriodic acid. As thus obtained, it is an amorphous substance, and very easily decomposed."

Solubility of Hydrastine.—Hydrastine is perfectly insoluble in water, or dilute alkaline solutions. Chloroform dissolves it freely, and is the best solvent we have found. It also dissolves in benzol, ether and cold alcohol, and freely in boiling alcohol. According to Prof. Power, it is insoluble in petroleum benzine, and its relative solubilities in the following liquids are as follows: One part of hydrastine in 1.75 parts of chloroform, in 15.70 parts of benzol, and in 120.27 parts of cold alcohol. Hydrastine unites with acids to form salts which are mostly soluble, tannic acid and picric acid forming insoluble combinations. These artificial salts are of acid reaction.

Salts of Hydrastine.—Muriate of hydrastine is used in medicine more extensively than any other salt, but the citrate is in some demand. These are both very soluble, and are colorless, although if a prolonged temperature be applied to the muriate, even if not above $82^\circ C$, it turns yellow.

* Ann. Chem. Pharm. **xxv**, p. 132.

† Gazz. Chim. Ital. **xiii**, pp. 329-342.

Alkalies decompose solutions of the salts of hydrastine, the alkaloid being precipitated.

These salts are best prepared by dissolving the acid in alcohol, and then adding an excess of hydrastine. After the solution ceases to take up the alkaloid, it is filtered and brought, if necessary, to a *very slight* acid reaction by means of the acid employed, and then evaporated at a low temperature to dryness. Salts of hydrastine and some of the volatile acids are not permanent, but decompose upon drying them, the acid escaping. Prof. Power calls attention to this fact with acetic acid. The composition of the salts of hydrastine are as follows: Muriate of hydrastine $C_{22}H_{23}NO_6.HCl$ (Mahla & Power). Double chloride of hydrastine and platinum $(C_{22}H_{23}NO_6.HCl)_2 + PtCl$ (Mahla & Power). Sulphate of hydrastine $(C_{22}H_{23}NO_6)_2.H_2SO_4$ (Power). Double chloride of hydrastine and gold $(C_{22}H_{23}NO_6.HCl)_2AuCl_3$ (Power).

YIELD OF HYDRASTINE AND BERBERINE FROM HYDRASTIS CANADENSIS.—The proportion in which these substances exist in hydrastis is quite variable. The season of year in which the rhizome is gathered, the method of curing the drug, and its age, being instrumental in varying the amounts of the alkaloids. If the drug is gathered in July or August, and quickly dried in the shade, it is in the best and most valuable condition. If it is gathered in the spring of the year, it is of inferior quality. Under any circumstance, carelessness in curing of the drug injures it, and may render it completely worthless. We have a constant experience in this variability of quality, and every year are compelled to reject considerable amounts that will not, in yield of alkaloids, repay the expense of working the material (see p. 95). That such a drug is not lost to the world may be inferred by consulting the table that we offer under powdered hydrastis, and it is to be hoped that in a day to come hydrastis (and other American drugs) may command a price in accordance with its real value.

The amount of berberine that exists in hydrastis is also influenced by the length of time the rhizome has been exposed to the atmosphere. It is constantly decomposing, even though the drug is stored in a comparatively protected position (see pp. 84 and 85). There seems to be a kind of decay that finally will result in the destruction of a considerable amount of berberine. In order to determine the progress with which this decay continues, we selected, 1870, pounds of freshly gathered, dried, hydrastis. Of this lot 500 pounds were worked at once, in a single percolator; 700 pounds in like manner were worked in twelve months, and 670 pounds in twenty-four months. Every precaution was taken to insure the same manipulation with each batch. The result was as follows:

The first batch, 500 pounds, yielded 9 pounds of mono-berberine sulphate, or 1.8 per cent.

" second " 700 " " $9\frac{3}{4}$ " " " " " 1.39 "

" third " 670 " " 9 " " " " " 1.34 "

Average of 1870 " being $27\frac{3}{4}$ " " " " " 1.48 "

(The average yield of commercial hydrastis is from 18 to 28 ounces of sulphate of berberine to the hundred pounds. It is not profitable to carry the extraction to the utmost limit, and from 18 to 24 ounces is a fair product.)

Hence it follows that it is not economy to store hydrastis from year to year, and manufacturers of these alkaloids have learned to work the drug while recent. Regarding the white alkaloid, hydrastine, we can not present a similar line of comparison. It is our custom to reserve several batches in crude form, and work the product of about 5,000 pounds of hydrastis at once. The yield of purified hydrastine, perfectly white crystals, averages from one-fourth of one per cent. to three fourths of one per cent. of the drug employed.

In this connection we will remark, that we have often noticed that batches of the drug which gave unusually low amounts of berberine, were liable to yield an increased amount of hydrastine. Mr. J. W. Forbes informs us that he has also noted this peculiarity, in working the drug in large amounts. In one instance (recorded by us in 1879) a lot of 1,000 pounds of ground hydrastis was moistened with water, and, by an accident, only half of it could be worked at once. The remainder became heated and changed in appearance (becoming greener in color), and when it was worked, the berberine proved to have mostly perished. The result, however, was a yield of hydrastine very much in excess of that obtained from the other half of the drug.

These circumstances, taken together, would suggest that there was a natural connection between the alkaloids, the indication being that, if such is the case, hydrastine is produced in the economy of the plant, by the disintegration of berberine. Prof. F. B. Power, in reviewing the analyses of these alkaloids, is inclined to view this relationship as complex, if it exists at all, and he writes: "It is also quite evident that there is no simple relationship between hydrastine and the alkaloid berberine, $C_{20}H_{17}NO_4$, such as exists, between the associate alkaloids, morphine and codeine, or caffeine and theobromine." It must be admitted that, if such changes occur, they are perfectly obscure and beyond the light of our present knowledge of the chemistry of these substances. It must also be recognized that there are several constituents in hydrastis that, together with their decomposition products, are unknown. In this connection we are sometimes led to compare together the plants that yield berberine, and it is usual to find the alkaloid associated with more or less of another alkaloid. It is not unreasonable to infer that a connection exists between them.

HALE'S "THIRD ALKALOID OF HYDRASTIS."—*History*.—This substance is recorded under the name "Hale's Third Alkaloid." While it is true that Mr. A. K. Hale* obtained a body from hydrastis that seemingly possessed properties that would distinguish it from both berberine and hydrastine, he did not really announce that it was a new alkaloid, as some persons seem to suppose. The heading of his paper, "Is there a Third Alkaloid in Hydrastis Canadensis," indicates that the author was undecided, and took this method to bring his experiments before the public, in order that subsequent investigators might determine the matter.

* American Journal of Pharmacy, 1873, p. 247

The material obtained by Mr. Hale was afterward identified by Mr. John C. Burt,* who gave a number of additional reactions. He also presented a micro-drawing of the sulphate, which we reproduce herewith (Fig. 43). Finally it was obtained by Mr. Herman Lerchen,† who affixed to it the name xanthopuccine.

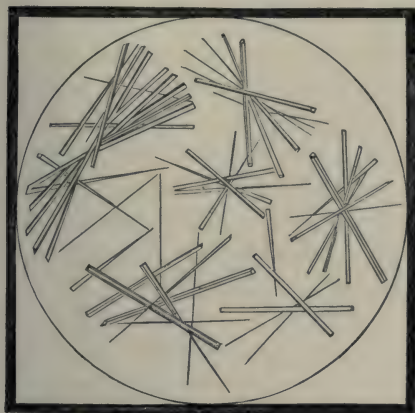


FIG. 43.

Crystals of the Sulphate of Hale's "Third Alkaloid" (magnified).‡

It would seem that these determinations should establish the fact that such an alkaloid existed, but we can not pass the matter without presenting evidence that we feel is worthy of consideration, and which leads us to view the impure substance obtained by these gentlemen as a mixture of berberine, hydrastine, and impurities of hydrastis. We will first review Mr. Hale's process, as follows: "I treated the powdered root of *Hydrastis canadensis* in a percolator with distilled water until the strength seemed to be exhausted; then I proceeded to remove the berberine as a hydrochlorate by the addition of hydrochloric acid. Removing this precipitate of hydrochlorate of berberine by filtration, I then proceeded to obtain the hydrastine by adding water of ammonia (10 per cent.) until a precipitate ceased to be thrown down. This precipitate I separated by filtration, and dissolved in and crystallized from alcohol, when, instead of hydrastine, as the books described it, I found that the characteristic prisms of hydrastine were colored by and intimately mixed with a yellow powder, which I supposed to be berberine that had not been thrown down as a hydrochlorate. Being thus a little disconcerted at not obtaining the result I hoped for, I made another percolate of the drug, and to the mother liquor of berberine I carefully added water of ammonia (10 per cent.) to the neutral point. The precipitate thus obtained I dissolved in and crystallized from alcohol, which furnished beautiful and well-defined prismatic crystals of hydrastine, free from yellow coloring matter at all resembling berberine.

"To the neutral mother liquor of hydrastine, I now added water of ammonia (10 per cent.) to a strong alkaline reaction. This gave me a yellow precipitate, which I separated, and found to correspond with the yellow powder above mentioned as accompanying the first attempt to obtain hydrastine, and to be darker in color than berberine."

Mr. Hale thought that this yellow substance might be a new alkaloid, and it has since been referred to as "Hale's Third Alkaloid."

Remarks.—An important point in the foregoing paper is the oversight

* American Journal of Pharmacy, 1875, p. 481.

† American Journal of Pharmacy, 1878, p. 470.

‡ Reproduced from American Journal of Pharmacy, Nov., 1875, as represented by Mr. John C. Burt.

made in neglecting to state whether the hydrochloric acid was added to the percolate until it was in *strong excess* (see p. 113).*

If it is only added until a decided acid reaction ensues, the natural combination in which the berberine exists is but partially overcome, and a large amount of berberine remains in solution. This is a feature that manufacturers of these alkaloids have to guard against, for if a considerable proportion of berberine is left in the mother liquid, it is largely thrown down with the hydrastine, and after being associated in this manner, its removal is difficult (see p. 134). Hence it follows that, if this precaution is not observed, the second precipitate by Mr. Hale's method is exactly as he describes it, but the yellow substance, as we have every reason to believe, is impure berberine.

The experimenter must also not overlook the fact that the alkaloids, hydrastine and berberine, are not the only substances thrown from solution by the *excess of ammonia*. A dark-colored, resinous body is also separated, and it adheres with some tenacity to the precipitate.† Thus it follows that, according to our views, also, and according to the results of our experience, a yellow precipitate may be obtained by means of Mr. Hale's process. Before introducing further testimony that we have to offer concerning the nature of this precipitate, we shall call particular attention to the following points:

Ist. When ammonia water is added to the percolate until this liquid is neutral, a portion only of the hydrastine precipitates. This percolate contains salts of calcium and aluminium (doubtless from adhering soil), and especially is the hydroxide of aluminium thrown down before the hydrastine, or with the first portions of it. Therefore it may happen that, by exercising care in neutralization, the larger share of the hydrastine may really remain in solution after the liquid ceases to affect litmus paper. The filtration of such a neutral liquid, and addition of excess of ammonia water to the filtrate, produces a precipitate of hydrastine that is much purer than the first precipitate; *providing the operator had taken the precaution to add hydrochloric acid enough to the original percolate to separate the berberine*, and had waited for it to separate before filtering the liquid from the precipitated hydrochlorate of berberine.

If, however, the hydrochlorate of berberine has been but partially thrown down, in consequence of an insufficient amount of hydrochloric acid having been added to the percolate, the second precipitate is of a deep yellow color, and may be mixed with yellow nodules of impure berberine.

If the percolate is very concentrated, the chloride of ammonium may be in sufficient amount to keep the liquid of acid reaction until nearly all of the hydrastine is precipitated.

* Mr. Lerchen, it is true, used the expression, "acidulating it strongly with hydrochloric acid," but he might have considered a decided acid reaction towards litmus as sufficient. In our experience, in order to precipitate all of the berberine possible (and it can not all be thrown down), hydrochloric acid to the extent of one-fourth the bulk of the percolate should be used.

† This substance is of considerable general interest, but it is not desirable to study it in this paper. Prof. E. Scheffer made an interesting line of experiments with it some years ago, and communicated his observations to us, but they have not been completed.

3rd. It is not safe to argue that because a distinct acid reaction (with HCl) will precipitate most of the berberine from an aqueous solution of pure berberine, and because a slight alkaline reaction is sufficient to throw down all of the hydrastine from an aqueous solution of pure hydrochlorate of hydrastine, these results will necessarily follow with an aqueous percolate of hydrastis. This liquid differs in solvent powers from pure water, and the natural combination in which these alkaloids exists is far stronger than any artificial union that we have been able to make by associating them together, after they have been purified. Indeed, we have no reason to hesitate in saying that we have failed to find satisfactory evidence to disprove the supposition that berberine and hydrastine exist in the rhizome as a double salt.

4th. If Mr. Hale's process of adding ammonia water in fractions, one to neutralization and the other to excess, produced two precipitates, why will not the immediate addition of a strong excess of ammonia throw down these two as a mixture? If such a mixture is obtained, it should contain the third alkaloid.

It has been our experience to work some thousands of pounds of hydrastis each year for the alkaloids. We obtain by this process a precipitate that contains hydrastine, berberine, and some other products, but we have not been able to purify the crystallizable yellow third alkaloid.

We have, also, time and again, followed Mr. Hale's directions, while working large amounts of the drug. We obtain a second precipitate, but by appropriate methods the yellow, bitter substance resolves itself into berberine.

Method of Separation.—There are several processes whereby this object can be accomplished, but one of the most successful is as follows:

Dry the precipitate, powder it, and then extract it with boiling alcohol and filter, which will leave the hydroxides of the alkaline earths; distil most of the alcohol and add the syrupy residue to several times its weight of water acidulated with sulphuric acid; filter and precipitate the filtrate with an excess of ammonia water; collect this precipitate, dry, and powder it. Then mix it with ten times its weight of cold alcohol and acidulate with sulphuric acid. The hydrastine dissolves, forming sulphate of hydrastine, while most of the berberine remains insoluble as sulphate of berberine. Collect and wash the precipitate, and purify it by re-crystallizations from hot alcohol. The product is sulphate of berberine. By collecting the residues, of the various steps, treating them again in the same manner, and repeating the operation, the crystallizable bitter yellow substance can be mostly separated, and will also be found to be berberine.

The hydrastine of the alcoholic solution contains still considerable berberine, which can be separated by repeated crystallizations.* By this method the two alkaloids can be separated from each other and from the associated im-

*We do not wish to be understood as saying that berberine is the only yellow substance present in the crude precipitate. It is not, for resinous and other bodies exist in it. To our experience, however, impure berberine is the only body that conforms to the third alkaloid.

purities; the berberine crystallized as sulphate of berberine, the hydrastine as the pure alkaloid. The result of one experiment of this kind, in which the precipitated crude hydrastine from several hundred pounds of hydrastis had been well washed with water, is recorded as follows:

Ninety-six ounces of crude precipitated hydrastine yielded $3\frac{1}{2}$ ounces of pure crystallized sulphate of berberine, and 79 ounces of crystallized hydrastine. The residues did not seem to contain any substance to conform with the third alkaloid. Thus it happens that each attempt we have made to obtain this substance has failed.

Naturally, others have been interested in the matter, and, although we have questioned manufacturers of alkaloids, none have yet to our knowledge obtained it. Prof. Edward S. Wayne informs us that he has not been successful. Mr. J. W. Forbes, who for some years worked hydrastis in considerable quantities, recently denied its existence.

In order to determine if by any oversight of manipulation we were being misled, we laid the result of our work before Prof. A. B. Prescott (Mr. A. K. Hale was in his class at the time he made his determination), and sent to Prof. Prescott a sufficient quantity of the percolate to go over the matter. His investigation did not terminate successfully, and he kindly wrote us to that effect; remarking that this alkaloid doubtless should be ranked among the substances that had been recorded without sufficient examination.

Finally, we made a lot of the crude precipitate according to Mr. Hale's process; purified it, and separated the yellow crystalline sulphate (berberine), from the white alkaloid (hydrastine); and then sent a portion of each in a perfectly pure form to Prof. F. B. Power; and the yellow sulphate to Prof. Virgil Coblenz. Neither of these gentlemen were aware of the method employed in producing them, and their combustions supported each other. The yellow substance had the composition $C_{20}H_{17}NO_4 \cdot H_2SO_4$; the white crystals were $C_{22}H_{23}NO_6$.

Having thus reviewed this subject, we can only answer Mr. Hale's query by saying that the substance obtained by his process is, in our opinion, a mixture, and that the yellow crystalline body is impure hydrochlorate of berberine. We think that Mr. Hale's error has been caused by the small amount of hydrastis used in the investigation, which we understand was less than five pounds, and we believe that, had he obtained the substance in sufficiently large quantities, he would, in purifying it, have discovered its complex nature.

Other Constituents of Hydrastis.—There are additional constituents, some of which are of considerable interest in a general way, but none have come into use in medicine.

A fluorescent body exists in very small amount, and adheres to the hydrastine with considerable tenacity, but is mostly separated during the last crystallizations. It is soluble in chloroform, and is more soluble than hydrastine, in cold alcohol. Its solution in cold alcohol is colorless, but with a

strong blue fluorescence. If we mistake not, it has been recorded that hydrastine possesses fluorescent properties, but our experience is to a contrary effect. When crude hydrastine in considerable amount is dissolved in acidulated water, and the solution is rendered alkaline with ammonia water, sufficient of this principle remains in solution to impart a deep blue color. Since it presents fluorescent properties in alkaline solution instead of in acid liquids, it may be the same as *æsculin*, which substance is asserted to be identical with the fluorescent principle of *Gelsemium sempervirens*.

Among the products that precipitate in making berberine and hydrastine when the liquid from which the alcohol was distilled is mixed with water, are a greenish oil and acid bodies that may prove of considerable interest, as shown by Prof. E. Scheffer, who had them under consideration some time ago.

Hydrastine and berberine exist in natural combination with at least one acid, of a purely sour taste, which we obtained in considerable amount as a syrupy solution, but just as we completed its purification our laboratory and all its contents were destroyed by fire. We made it by throwing out the sulphuric acid from the refuse of sulphate of berberine, by means of carbonate of barium, and after purifying the barium salt of the vegetable acid, decomposing it with an exact amount of sulphuric acid. We shall repeat the experiment.

It is to be presumed that some of the other products of *hydrastis* will prove of great interest to the investigator.

Powdered Hydrastis.—The consideration of this substance would naturally follow that of the drug, but we have thought it best to first introduce the constituents of *hydrastis*, inasmuch as the quality of the powdered rhizome really depends upon the proportions of these substances. The history of our powdered drugs is, in many instances, not an inviting one, and *hydrastis* seems not to have escaped the stigma that is affixed to many other substances of this nature. It is true that, as a rule, the price of the rhizome is but a trifle, and yet it may perhaps be safely said that where there is a desire to cheapen a drug, it matters little how cheap it may be, something can be found to mix with it that is less expensive. However, we do not accept that an inferior powder must necessarily be deficient in quality from an intentional adulteration. The remarks we have made in the preceding pages, regarding the variation in quality of crude *hydrastis* will indicate that the powder may really be from the rhizome of *hydrastis*; unmixed with extraneous substances and still be of inferior quality. If a worthless drug is employed the powder can not be an improvement on the crude material. It is true, we think, that the inferior qualities of many American drugs may find their way into commercial powders. This, doubtless, was true to a greater extent formerly than at present. In our opinion wholesale druggists generally desire to furnish the better qualities of all drugs, crude or powdered. That they can not always do so is perhaps largely because it is understood too often that the value of a given drug is the same, regardless of its quality; and none will

deny the strong competition that the price brings to bear on dealers. Pharmacists are, in our opinion, more careful than formerly, and by the united efforts of these two bodies of men, pharmacists and jobbers, we doubt not that the progress towards a better day will continue. If we are correct, the present day is far in advance of a few years ago. We doubt if the time has ever been in the history of this country (since pharmacists commenced depending on dealers for their powdered drugs), that the qualities were equal to those of the present. The causes for an inferior powdered hydrastis, aside from intentional admixture, are the same as for the inferior drug. In considering the powdered hydrastis of commerce, should we, therefore, compare it with the average quality of the crude material such as is accepted without objection by a good pharmacist, or, with the choicest that can be obtained?

We must now leave this matter with the reader to judge as to the attention that is given this subject by pharmacists at large; but it seems to us that a dealer in a substance like powdered hydrastis can not be very severely criticised for supplying an inferior powder (shown to be inferior by analysis), if the same quality of crude hydrastis is accepted without objection by those who should act as authorities. It would be out of place for us to argue the question here, as to whether the standard of powdered hydrastis should be higher than that of the drug, but this phase of the question can with propriety be applied to other American drugs. It is a subject that will confront us before many years.

The description of hydrastis, as given in the United States Pharmacopœia, is not such as can afford a standard of comparison. There is no recognition of the powdered drug in that work, and no standard for the crude other than that derived from a description of the physical appearances.

In 1882, Mr. C. B. Allaire presented a report to the American Pharmaceutical Association, in which he records the microscopic examination of eleven specimens of commercial powdered hydrastis, all of which were adulterated. Mr. Allaire informs us, in a communication, that many of these specimens had been intentionally mixed with extraneous substances, but that in some instances the admixture was an earth that might have been present in the unwashed drug. However, it constituted such a large percentage that it could only be viewed in the light of an adulterant.

In 1883, Mr. E. C. Bassett, then in the chemical laboratory of the University of Michigan, examined, by the microscope, eighteen specimens of commercial powdered hydrastis. Of these, twelve were unadulterated; three contained a little curcuma as a coloring; one was about one fifth curcuma; one a mixture of curcuma and bean starch; and one curcuma and a foreign root that could not be identified. Thus it appears that two-thirds of these specimens were free from admixtures.

However, while the microscope will detect such foreign substances as may be mechanically added to the powdered drug, or powdered with it, it is obvious that it can not indicate the comparative value of the specimens that

are unmixed; and it is essential that a chemical method of detection be employed under such circumstances. That it can be made readily and simply is demonstrated by the nature of the constituents, and as at present the berberine is considered the important one, a comparison of the proportions of berberine is probably our best method of standardizing the drug.*

Appearance of Powdered Hydrastis.—This powder is not a bright yellow. Upon the contrary, it is usually of a dull yellowish hue, and often with a slight tinge of green. The brown surface of the rhizome and rootlets, and the decayed fragments that are always more or less intermixed with the crude drug, destroying the rich yellow that would otherwise be a characteristic; and thus, if commercial powdered hydrastis is a bright yellow, it is perhaps open to suspicion. Powdered hydrastis has the characteristic odor of the rhizome, as described on page 85 of this publication.

Estimation of Berberine in Powdered Hydrastis.—The remarks that we have made in the preceding pages on the berberine subject will indicate that a method of estimating this alkaloid under one condition may perhaps be unreliable under certain other circumstances.

We shall not consume time in this place with the difficulties that accompany the processes that we have tried; for in the future we must consider this alkaloid in a broader field than it occupies in this one plant, and our remarks will then be more pertinent. The fact that it is associated with one, and perhaps, other alkaloids, necessitates a scheme that will disentangle it from such associations or combinations, and it is desirable also that the scheme should be as simple as possible and as easily applied as is practicable. We prefer the following process: †

Reduce the hydrastis to an impalpable powder, if it is not already in that condition, and then macerate one part of the powder with eleven parts of officinal alcohol, shaking often. After four days permit the powder to subside completely, and decant the overlying liquid. Add to the magma sufficient alcohol to produce the original bulk, and repeat the operation. Repeat the maceration with a third portion of alcohol and decant as before. Mix these decanted liquids, and after twelve hours filter them, washing the filter paper with a little alcohol. Add to the filtrate one-third its bulk of officinal sulphuric ether, and then hydrochloric acid to the extent of three-tenths, and sulphuric acid to the extent of one-tenth the weight of the hydrastis employed. Place the liquid, after mixing well, in a cool place, and after forty-eight hours collect the crystalline precipitate on a filter paper and wash it with a mixture of equal parts of sulphuric ether and alcohol until the crystals are free from uncombined acid; then dry it at a temperature of 125° Fah. and weigh it.

* Since this sentence was in type, the investigations of eminent medical authorities have drawn attention particularly to *Hydrastine*, and the indications are that this alkaloid may become the most important constituent.

† The berberine is not as completely extracted by this as by a process that we shall introduce at a future day; but for simplicity this process is desirable.

This process practically abstracts from the hydrastis its berberine, and precipitates it almost completely and as a nearly pure salt. It is true that some may prefer to employ percolation, but to our experience, in unskillful hands the process of maceration is less likely to be followed by variation in product. We do not deny that some berberine remains in the drug, for by another process the extraction is more perfect; but this process will answer as a method of comparison.

The addition of the sulphuric ether to the alcoholic solution produces a menstruum in which, if acidulated as we direct, the hydrochlorate of berberine is so nearly insoluble as to leave no trace of bitterness after separation of the salt.* It must be also observed that, while this process is capable of precipitating a larger amount of berberine than can be obtained by the process we use in making hydrochlorate of berberine (see p. 113), it is less economical on a manufacturing scale, for the increased yield is more than counterbalanced by the expense of the ethereal menstruum; and at the usual price of hydrastis it is false economy to carry the extraction of the drug beyond a limit that is sufficient to repay in yield of berberine, the loss of material and the time consumed. Hence, in connection with our remarks on page 137, in which we present the average economical yield of berberine from ordinary commercial hydrastis, we record the following table, which gives us the comparative qualities of powdered hydrastis, as found in the American market: †.

TABLE SHOWING THE EXAMINATION OF FORTY-NINE SPECIMENS OF COMMERCIAL POWDERED HYDRASTIS.

Specimen	1	yielded from 60 parts	Powdered Hydrastis	1.34	parts Berberine Hydrochlorate, equalling 2.23 per cent.				
do	2	do	do	1.335	do	do	do	2.22	do
do	3	do	do	1.26	do	do	do	2.10	do
do	4	do	do	1.25	do	do	do	2.08	do
do	5	do	do	1.25	do	do	do	2.08	do
do	6	do	do	1.23	do	do	do	2.05	do
do	7	do	do	1.21	do	do	do	2.04	do
do	8	do	do	1.19	do	do	do	1.98	do
do	9	do	do	1.19	do	do	do	1.98	do
do	10	do	do	1.18	do	do	do	1.96	do
do	11	do	do	1.16	do	do	do	1.93	do
do	12	do	do	1.15	do	do	do	1.91	do
do	13	do	do	1.12	do	do	do	1.86	do
do	14	do	do	1.12	do	do	do	1.86	do
do	15	do	do	1.10	do	do	do	1.83	do
do	16	do	do	1.10	do	do	do	1.83	do
do	17	do	do	1.10	do	do	do	1.83	do
do	18	do	do	1.08	do	do	do	1.80	do
do	19	do	do	1.08	do	do	do	1.80	do
do	20	do	do	1.08	do	do	do	1.80	do
do	21	do	do	1.08	do	do	do	1.80	do
do	22	do	do	1.08	do	do	do	1.80	do
do	23	do	do	1.05	do	do	do	1.75	do
do	24	do	do	1.04	do	do	do	1.73	do
do	25	do	do	1.04	do	do	do	1.73	do
do	26	do	do	1.01	do	do	do	1.68	do

* Hydrastis contains coloring matters besides berberine, hence the liquid is not decolorized.

† This line of experiment was instituted by Mr. Leslie Soule in our laboratory, the method of investigation being in accordance with the scheme announced on preceding page. The specimens came from Indianapolis, Philadelphia, Little Rock, Louisville, Zanesville, South Bend, Ind., Pottsville, Pa., Chillicothe, O., and Lynn, Mass. Equal amounts of each were operated upon, and all carried simultaneously until the work was completed.

Specimen 27 yielded from 60 parts Powdered Hydrastis 0.98 parts Berberine Hydrochlorate, equalling 1.63 per cent.									
do	28	do	do	do	0.97	do	do	do	1.61 do
do	29	do	do	do	0.97	do	do	do	1.61 do
do	30	do	do	do	0.97	do	do	do	1.61 do
do	31	do	do	do	0.94	do	do	do	1.56 do
do	32	do	do	do	0.94	do	do	do	1.56 do
do	33	do	do	do	0.91	do	do	do	1.51 do
do	34	do	do	do	0.90	do	do	do	1.50 do
do	35	do	do	do	0.85	do	do	do	1.41 do
do	36	do	do	do	0.83	do	do	do	1.37 do
do	37	do	do	do	0.83	do	do	do	1.37 do
do	38	do	do	do	0.79	do	do	do	1.31 do
do	39	do	do	do	0.70	do	do	do	1.16 do
do	40	do	do	do	0.70	do	do	do	1.16 do
do	41	do	do	do	0.62	do	do	do	1.03 do
do	42	do	do	do	0.61	do	do	do	1.01 do
do	43	do	do	do	0.57	do	do	do	0.95 do
do	44	do	do	do	0.54	do	do	do	0.90 do
do	45	do	do	do	0.35	do	do	do	0.58 do
do	46	do	do	do	0.31	do	do	do	0.51 do
do	47	do	do	do	0.24	do	do	do	0.40 do
do	48	do	do	do	0.21	do	do	do	0.35 do
do	49	do	do	do	0.205	do	do	do	0.34 do

REMARKS.—It will be observed that the yield of hydrochlorate of berberine varies from 2.23 per cent. to 0.34 per cent. Twenty-seven of the specimens were below the average working yield (1.8 per cent.) of fresh commercial hydrastis, as recorded on page 137, and seventeen specimens were above it. Five of the specimens gave the exact amount. It may safely be said that the specimens below this were inferior, for a quality of hydrastis that yields 1.8 per cent. by our working process will assay considerably better; and our experience is that the average assay of berberine hydrochlorate is not less than 2 per cent. That it may be above this is shown by the first seven specimens of our table. Averaging, however, those recorded above 1.8 per cent., we have a result of 1.98½. The powdered hydrastis of commerce should, in our opinion, not only reach this figure by this process, but assay 2 per cent. Allowing, however, for age and imperfect rhizomes, which some may contend should have a consideration, we may possibly lower the figure to 1.95 per cent. It will be observed that of the 49 specimens assayed but 10 reached this standard and 7 were actually less than one per cent. Of these very low specimens we can only say that, even though gathered in early spring-time and imperfectly cured, we have never met with so small a yield of berberine from hydrastis, and there is but one inference in regard to the matter. The pharmacist who purchases such a powder pays an exorbitant price when quality is considered. The physician who prescribes such a drug can not hope for a positive action.

To sum up, accepting the berberine as a standard, commercial powdered hydrastis as found in the drug market of this country is nearly four-fifths below grade, and a very considerable porportion of it is certainly adulterated with foreign bodies, or it may be with the dried and powdered hydrastis muck from which the alkaloids have been extracted.

*The Detection of Curcuma in Powdered Hydrastis.**—Solution of caustic potassa with curcuma gives an immediate deep orange brown coloration which, in the course of a few hours, assumes a decided purple hue. With pure powdered hydrastis no change occurs. In mixtures of the two the deepness of both the primal and ultimate colors is in direct proportion to the curcuma. Hydrochloric acid furnishes a somewhat lighter orange red which slowly fades to a pink with curcuma, but no coloration whatever with the pure

* Mr. E. S. Ely made in our laboratory a series of examinations of hydrastis, curcuma, and admixtures of hydrastis with curcuma and such indigenous drugs as we have found associated with hydrastis. This interesting paper is to be found in the Druggists' Circular, May, 1885, and in acknowledgment of his work, and that of Mr. Soule, we herewith extend our thanks for their value to this publication. The necessity for the introduction of the test for curcuma is evident from Mr. E. C. Bassett's investigations (see page 144).

hydrastis. In mixtures of the two the same colors are produced as with curcuma alone, but varying in density according to the percentage of the latter. The caustic potassa solution is much the more delicate test of the two, giving immediate and distinct colorations where the acid entirely failed. The best method to conduct the foregoing tests is to place about a drachm of the suspected powder upon white filtering paper, and then carefully drop sulphuric ether upon it until the coloring matter is well extracted and diffused over the surface beyond the powder. The ether is allowed to evaporate, when a drop of caustic potassa or hydrochloric acid is added to the colored portion of the paper. A coloration will follow if curcuma is present, as described under tincture of hydrastis.

This test is so delicate as to actually show an admixture of one part of curcuma with 10,000 parts of hydrastis, a perceptible delicate red color appearing at the margin of the spreading alkaline liquid as it passes through the ether stain.

The Detection of Curcuma in Tincture of Hydrastis.—Saturate white filtering paper with the tincture, and allow it to dry. Upon the addition of solution of caustic potassa an immediate orange brown color is produced which gradually assumes a purple hue if curcuma is present, the colors being more or less deep according to the percentage of the latter. Tincture of pure hydrastis is not affected when treated likewise. If a small amount of the suspected tincture be placed in a test tube and caustic potassa added, the orange brown coloration quickly appears if the curcuma is present, even where the paper test fails. Pure tincture of hydrastis, under the same conditions, is not discolored, but rendered turbid, owing to an alkaloidal disturbance. Concentrated hydrochloric acid colors curcuma paper prepared from the tincture a deep reddish brown, which gradually fades to a pink. The hydrastis paper furnishes no coloration. In the test tube, hydrochloric acid furnishes an intense cherry red liquid with the curcuma tincture, but only renders the tincture of hydrastis slightly turbid, and finally a crystalline mass of hydrochlorate of berberine separates, with no coloration. In each of these tests upon mixtures of the tinctures of hydrastis and curcuma, the colorations and their intensity are directly proportioned to the percentages of curcuma.

These reactions are conclusive, and may be summed up as follows: Neither hydrastis nor tincture of hydrastis affords the color reactions of curcuma or tincture of curcuma. If celastrus root be mixed with the hydrastis, the potash reactions of curcuma may be masked, as the former affords a black or deep brown coloration, according to its percentage, that might predominate the orange brown and purple of curcuma. In this case the hydrochloric acid test serves to detect the latter, since with it the celastrus gives but a very slight reddish coloration, with no pink after-color.

We scarcely consider it necessary to consume more time with this subject. Our work supports the report of Mr. Allaire and Mr. Bassett, and we doubt not that if our pharmacopœia revisers find it advisable to standardize hydras-

tis, the act will be followed by an improvement in the quality of the commercial drug.

PHARMACEUTICAL PREPARATIONS.—*Fluid Extract of Hydrastis*.—The present officinal process for making this fluid extract is as follows:

“Hydrastis, in No. 60 powder, one hundred grammes, alcohol, water, each a sufficient quantity to make one hundred cubic centimeters.

“Mix three parts of alcohol with one part of water, and, having moistened the powder with thirty grammes of the mixture, pack it firmly in a cylindrical percolator; then add enough of the menstruum to saturate the powder and leave a stratum above it. When the liquid begins to drop from the percolator, close the lower orifice, and, having closely covered the percolator, macerate for forty-eight hours. Then allow the percolation to proceed, gradually adding menstruum, until the hydrastis is exhausted. Reserve the first eighty-five cubic centimeters of the percolate. By means of a water-bath, distil off the alcohol from the remainder, and evaporate the residue to a soft extract; dissolve this in the reserved portion, and add enough menstruum to make the fluid extract measure 100 cubic centimeters.”—U. S. P., 1880.

This produces a very bitter, dark-colored liquid of a reddish yellow color in thin layer, and upon shaking the bottle that contains it, a deep yellow stain remains where the liquid adheres to the glass. When freshly prepared it is transparent, but it sometimes becomes of a muddy appearance by age. If it be prepared of prime hydrastis, and perfectly percolated, a deposit follows, often within a few days of the time of its preparation. In cool weather, especially if the fluid extract was prepared (as it should have been) in a warm location, this precipitate is abundant, forming a deposit that will perhaps occupy one-fourth the bulk of the liquid. This sediment is largely made up of yellow crystals, and in very cold weather beautiful spangles of crystals form upon the inside of the container. This crystalline sediment is a berberine compound, and in accordance with its production the berberine value of the solution decreases. For this reason, a fluid extract of hydrastis that has precipitated in this manner should be shaken before using it. If it be heated, the sediment mostly dissolves, to re-precipitate when cooled. Taken altogether, we do not feel that the officinal fluid extract of hydrastis is a very acceptable pharmaceutical, but by the crude and simple method of percolation it may be difficult to obtain a more satisfactory liquid by using any menstruum that is a mixture of alcohol and water. Within three weeks' time a specimen that had been made under our direction, very carefully, from prime hydrastis, lost 18.85 per cent. of its berberine by precipitation.* Hence we should not expect the commercial fluid extracts of hydrastis to be of uniform strength even when made of standard hydrastis.

Test.—Transparent fluid extract of hydrastis, when added to a mixture

* Mr. W. M. Schmitt made, in our laboratory, a number of determinations of the berberine in commercial fluid extracts. This paper will be found in the *Pharmaceutical Record* during 1885, and is of considerable interest. The variation in percentage of berberine announced by us as taking place inside of three weeks from the time of preparation was in a standard fluid extract made by Mr. Schmitt.

of alcohol three parts and water one part, should form a transparent mixture. It should produce a yellow crystalline precipitate (hydrochlorate of berberine) when mixed with one-fourth its bulk of hydrochloric acid; and a dirty yellowish brown sediment (impure hydrastine) when mixed with an excess of ammonia water. It should yield at least two per cent. of berberine salts by the following assay process:

Mix one fluid ounce of fluid extract of hydrastis with two fluid ounces of a mixture of equal bulks of sulphuric ether and alcohol, and after twenty-four hours decant the overlying liquid. Dissolve the precipitate in two fluid drachms of dilute alcohol, and add one fluid ounce of a mixture of alcohol two parts and sulphuric ether one part, by measure. Allow to stand twenty-four hours, and again decant the overlying liquid and mix with the reserved portion. Then treat the precipitate with one fluid drachm of the above mixture for three successive times, mix with the reserve and filter the mixture. To the filtrate add two fluid drachms of muriatic acid and one-half fluid drachm of sulphuric acid. After an exposure of twenty-four hours in a cool location, separate the crystalline precipitate by means of a filter paper, wash it with a mixture of equal bulks of alcohol and sulphuric ether, until the free acid is removed; then dry it by exposure in a drying closet to a temperature of 125° Fah. and weigh immediately. The yield should not be less than two per cent. of the hydrastis employed; it may reach three and one-half per cent.* Curcuma is detected by the methods given under powdered hydrastis, using the fluid extract instead of the tincture.

Fluid Extract of Hydrastis without Alcohol.—We object to the foregoing name. If applied to the substances originally introduced, and which the liquids sold under the above name are designed to imitate, it is a misnomer. They certainly were not fluid extracts. The earliest record that we have of such a preparation was about 1874, when the writer prepared for topical purposes a liquid that was to be free from alcohol, and transparent. It gave excellent satisfaction, and came into quite general use, finally being thrown upon the market under various names to distinguish it from the officinal fluid extract. We believe it to be fully as efficacious, and a preferable pharmaceutical, as it is more permanent, and miscible without precipitation with either syrup, glycerine, water, wine or alcohol.

Preparation.—Percolate powdered hydrastis with officinal alcohol until the hydrastis is exhausted. Add to the percolate one-third as much by weight of water as there was of the hydrastis, and evaporate the alcohol. After all the alcohol is driven off, mix with the residue enough cold water to bring the entire weight to two-thirds that of the hydrastis. After twenty-four hours, filter the liquid, and add to the filtrate enough glycerine to bring to the weight of the hydrastis employed.

* If the hydrastis is prime, and the percolation complete, a larger amount of this berberine salt is obtained than by our process (p. 145) for assaying powdered hydrastis. The berberine salt is not as pure, however, and we usually prefer the other method for a direct estimation of hydrastis.

It will be observed that by this simple process the desirable constituents of the hydrastis are extracted by means of the alcohol, without the gums and inert extractive matters; although the oil and resins are associated in the percolate. The subsequent evaporation of the alcohol and admixture of the residue with water precipitates the oils and resins which are then separated by filtration. Thus a very pure solution of the natural alkaloidal constituents of hydrastis is obtained, and the addition of the glycerine produces a menstruum from which they do not separate by standing, and which will not ferment. This pharmaceutical, in our opinion, and we have made some thousands of pounds of it, is preferable to the officinal fluid extract. It can be administered whenever that substance is indicated and as an injection, or wash, is admissible in many cases when the fluid extract can not be employed. We hope that a similar preparation may become officinal. It will be observed that the process is such as to forbid the name fluid extract, unless the product is made officinal under that term, and we believe that the proper location is among the liquors. We therefore prefer the name *Liquid Hydrastis*, having used it for many years. We reproduce our description of this pharmaceutical as follows:

"Liquid hydrastis has a beautiful, deep yellow color, and when shaken, stains the bottle clear yellow. The taste is bitter, but not unpleasant and nauseating, like some bitter drugs. There is no odor of alcohol, none being present, but it possesses the exact odor of fresh powdered hydrastis. It will mix with water, glycerine, wine, or syrups, in any and all proportions, and the mixtures will not become turbid. It will not ferment, and the freezing point is much less than that of water. It contains all of the alkaloids and acids of hydrastis, in their natural combinations."

Tincture of Hydrastis.—This is officinal, as follows: "Hydrastis, in No. 60 powder, twenty parts. Diluted alcohol, a sufficient quantity. To make one hundred parts.

"Moisten the powder with fifteen parts of diluted alcohol, and macerate for twenty-four hours; then pack it in a cylindrical percolator, and gradually pour diluted alcohol upon it, until one hundred parts of tincture are obtained."
—U. S. P., 1880.

The chief feature in connection with this pharmaceutical is the difference in menstruum used in it and that of fluid extract of hydrastis. If this tincture were designed for a different purpose than the fluid extract, this change would perhaps be obvious; or, if the menstruum of either were incapable of extracting the increased, or decreased amount of hydrastis of the other. In our opinion, tincture of hydrastis should be made of the menstruum employed in producing the fluid extract, for the increased amount of alcohol will not affect its administration.*

* When admissible, we favor a uniformity in the menstruum that is used in making both the tincture and fluid extract of a given drug. Conditions may possibly exist in which a break is necessary, but we think that as a rule it will be found that a menstruum best adapted to making one of these preparations is the one to use with the other.

Essence of Hydrastis.*—The Pharmacopœa Homœopathica Polyglotta recognizes this preparation as follows: The rhizome (fresh root) is pounded to a fine pulp and weighed. "Then two parts by weight of strong alcohol are taken, and after thoroughly mixing the pulp with one-sixth part of it, the rest of the alcohol is added. After having stirred the whole well, and having filled it into a well-stoppered bottle, let it stand for eight days in a dark, cool place. The essence is then separated by decanting, straining and filtering."

MEDICAL HISTORY.—The root of this plant was highly prized as a dye by the North American Indians on account of its yellow coloring matter, and also for its medicinal value; but Kalm, in 1772, Cutler, in his *Indigenous Vegetables*, 1783, and Schoepf, in his *Materia Medica Americana*, 1785, overlooked it. This seems remarkable when we consider the important position that hydrastis occupied with the various tribes of Indians and with our settlers. Although the Indians introduced hydrastis to the whites (see medical properties), and it has always been a domestic remedy, it was reserved for Barton to bring the plant before the medical profession. The first medical reference that we have been able to find occurs in Barton's *Collections for a Vegetable Materia Medica*, 1798 (part first), wherein credit for its introduction is given the Cherokee Indians. In the third part of this work, page 13 (1804), he devotes considerable attention to the drug, and mentions the fact that it "supplies us with one of the most brilliant yellow colors with which we are acquainted." From this date until the appearance of Rafinesque's *Medical Flora of the United States*, 1828, nothing of importance was published in medical literature, and nothing added to Barton's remarks. His statements were either copied verbatim or condensed by writers upon *materia medica*, although few gave him any credit for his work. † Rafinesque next (1828) devoted considerable space to this plant, and produced a rude figure of it. ‡

In 1833 a paper from the editor of the Thomsonian Recorder appeared in that work (Vol. I., p. 397) which was the most important communication we have been enabled to find to that date. This paper gave a synopsis of the previously ascribed values of hydrastis, and added the uses Dr. Thomson made of it and the position it occupied in Thomsonian practice. §

* This essence, or mother tincture as it is called, of hydrastis is the only pharmaceutical preparation of hydrastis used in homœopathic medicine, and peculiar to homœopaths. From it, in the usual manner, their dilutions are made. Homœopathic physicians use the alkaloidal salts defined by us in preceding pages.

† Captain Lewis (of the Lewis and Clarke expedition) attached a paper to his herbarium specimens of *Hydrastis canadensis*, May 24th, 1804, in which attention is called to the fact that "it is said to be a sovereign remedy" in eye diseases, and prized by the inhabitants of the country where it grows. This paper was not published until 1834, when it appeared in the *American Journal of Pharmacy*, p. 201.

‡ This figure has been reproduced, time and again, by subsequent authors, and in no instance have we found a credit given to Rafinesque's work. His engravings seem to have been considered as common property, and few, if any copyists, had the courtesy to acknowledge the source.

§ Hydrastis seems not to have been a conspicuous remedy of the early Thomsonians. It was mentioned in a paper which appeared in the Thomsonian Recorder, 1834, p. 313, entitled, "The *Materia Medica* of Dr. Samuel Thomson's Guide and Narrative, being a correct catalogue of all the plants recommended by him," but it occupied little space in his works. Many of Thomson's early followers scarcely recognized it. Comfort's "Practice of Medicine on Thomsonian Principles" gives but a brief notice of hydrastis.

Beach introduced hydrastis into the first edition of his *American Practice of Medicine* (1833), and it has always been an important member of the *materia medica* of his followers.*

The *United States Dispensatory*, first edition, 1833, omitted hydrastis, but the second edition, 1834, gave it a brief consideration in the appendix.†

Between this date and 1852 the standard works upon *materia medica* usually noticed the plant, but very briefly, and really added nothing to the preceding literature. Short extracts were usually made from the works of Barton, Rafinesque, Beach, or Thomson, the selection of authorities being usually in accordance with the affiliations of each writer. Hydrastis had, however, at this time become a recognized remedy. In 1852 King's *Eclectic Dispensatory* appeared, and hydrastis was highly recommended as an Eclectic remedy, in the following language: "This remedy is peculiar to Eclectics, and ranks among their best articles." In that work the medical uses and properties of hydrastis were prominently drawn by Prof. King, thus bringing the plant conspicuously before the Eclectic section of the medical profession. About this date interest was excited in certain products of the plant which were at that time commencing to be liberally advertised. These facts, together with frequent contributions from physicians who wrote for the *Eclectic Medical Journal of Cincinnati*, produced an extensive demand for the plant and its products, although this demand was almost exclusively among Eclectics. Hydrastis rapidly became more popular, however, and soon overstepped the bounds of sectionalism. In 1860 it was made officinal in the *United States Pharmacopœia*.

In the Regular section of medicine, Prof. Roberts Bartholow has given considerable attention to hydrastis, as is indicated by his paper on the subject in the various editions of his *Materia Medica*, and our readers are indebted to this author for a communication that follows regarding the uses of hydrastis. In 1862 hydrastis excited interest sufficient to merit a paper from Prof. Bentley, of England, under the heading, "New American Drugs," which appeared in the *Pharmaceutical Journal and Transactions*, 1862, p. 540, but which was mainly devoted to a consideration of the proximate principles of the plant. This is the only important foreign contribution we have in the early medical literature pertaining to this plant, although in 1873 Dr. Van der Espt presented a lengthy paper to the Royal Society of Medicine and National Sciences, Brussels, Belgium, without, however, adding any new facts; and recently the plant has excited some little attention in Germany.‡ It has

* Hydrastis was in reality brought out by the Eclectics, and is often known as an Eclectic Remedy. Prof. John King has valued it since 1833. The late Wm. S. Merrell introduced its products perhaps more extensively than any other person. In connection with this subject, it should be recognized that Dr. Walter Beach and the early Eclectics worked together.

† This unimportant notice passed unchanged through nine editions of that recognized authority, and was only slightly enlarged in the tenth edition, 1854, occupying still a position in the appendix. In the twelfth edition, however, it was placed in the primary department, the plant having been honored by an officinal position in the *Pharmacopœia* of 1860.

‡ The recent literature upon the therapeutics of hydrastis will be considered in the medical contributions of our contributors.

steadily grown in favor, all schools of medicine use it, and many members of each school value it very highly. The converse is also true, and many physicians neglect it, while others do not use it at all.

MEDICAL PROPERTIES (HISTORY).—In 1798 Prof. B. S. Barton issued the first part of his "Collections for an essay towards a Materia Medica of the United States." In it he writes, p. 9: "I am informed that the Cherake† cure it [cancer] with a plant which is thought to be *Hydrastis canadensis*." In the third part of his "Collections," 1804, he again refers to *hydrastis*: "The root of this plant is a very powerful bitter" (p. 13), and says (p. 14): "The *hydrastis* is a popular remedy in some parts of the United States. A spirituous infusion of the root is employed as a tonic bitter in the western parts of Pennsylvania, etc., and there can be no doubt that both in this and in other shapes, our medicine may be used with much advantage. An infusion of the root in cold water is also employed as a wash in inflammations of the eyes."†

Hand (House Surgeon, 1820,) adds: "It may be given in form of powder or of strong tea made by boiling, in indigestion, the secondary stages of low fevers, and all cases of weakness in general."

Rafinesque's Medical Flora, 1828, Vol. I., pp. 253 and 254, supports the foregoing, and in addition states that "they [natives] also employ it for sore legs and many external complaints as a topical tonic. Internally, in infusion or tincture, in disorders of the stomach, the liver, etc. It appears to be slightly narcotic and available in many other disorders. Some Indians employ it as a diuretic, stimulant and escharotic, using the powder for blistering§ and the infusion for dropsy." In Elisha Smith's Botanic Physician, 1830, we find several compounds containing *hydrastis*, to-wit: "Stimulating Cathartic Powders," "Bone's Bitters," and "Tonic Powders." Howard's Improved System of Botanic Medicine, 1832, p. 327, recommends it, also, in dyspepsia. Beach (1833), American Practice of Medicine, states that in connection with tonic properties it is "at the same time laxative, which makes it very appropriate in dyspeptic disorders." Next, the edition of the Thomsonian Recorder of 1833, p. 398, reviewed the medical properties as previously announced by others, and added to them as follows: "The importance of this article, taken in teaspoonful doses, for the relief and removal of bowel complaints in children should be extensively known. It is not only a corrector of the stomach, a regulator of the bowels, and a vermifuge for children, but it is an admirable remedy for the peculiar sickness attendant on females during their periods of utero-gestation, called morning sickness. It admirably relieves stomachic oppression, nausea, and heart-burn." Of the use of *hydrastis* in

* Cherokee Indians.—Ed.

† Rafinesque's Medical Flora, Vol. I., 1828, p. 253, adds: "It is considered a specific by the Indians for that disorder." Captain Lewis, 1804, supports the above, saying: "It is said to be a sovereign remedy in a disorder common to the inhabitants of the country where found, usually termed *sore eyes*."

‡ This must be a mistake; *phytolacca*, or *sanguinaria*, will blister, but *hydrastis* can not be used for this purpose.

sore eyes he writes: "It is not a decoction of the dried root in boiling water that relieves ophthalmia, but is the freshly dug root, well cleansed and bruised, and infused in cold, soft water, that is to be particularly relied upon."* Sanborn's Medical Botany, 1835, p. 63, states that the Indians use hydrastis as a diuretic. If the root be chewed it will cure white aphtha or ulcers in the mouth.† Kost (Elements of Materia Medica and Therapeutics) states that it is good as an application in infusion to inflammations of the mucous tissues, leucorrhœa, blenorrhœa, etc., and is of value in erysipelas. Dunglison (Medical Dictionary, 1852, p. 450) is the authority for a statement to the effect that in Kentucky hydrastis is used as an outward application in wounds.‡

In 1852 Prof. John King issued the first edition of his dispensatory, under the title, "The Eclectic Dispensatory of the United States of America," and therein gave the medicinal uses of hydrastis a more careful review than had previously been awarded, although many of the values that early writers had ascribed to the plant were omitted as being overdrawn.§ The indications for the administration and use of the drug and its preparations were carefully discussed in that work, and the remedy was thereby brought legitimately before the Eclectic branch of the medical profession (see Medical History), and in consequence of its general adoption by Eclectics it was from that time generally known as an Eclectic medicine. King was first, that we can find recorded, to recommend the plant in gleet and chronic gonorrhœa, and he wrote: "I have used this preparation likewise with much success in incipient stricture, spermatorrhea, and inflammation and ulceration of the internal coat of the bladder." From that time hydrastis was a popular remedy. It became officinal in 1860, and it now occupies a higher position than at any previous day, and the Homœopathic branch of the medical profession also use it extensively, as is shown by Prof. Hale's paper on the subject.

* In contradiction to the fresh root part of this statement we quote from Captain Lewis, 1804. In speaking of the eye troubles of the settlers, he remarks as follows: "This disease is a violent inflammation of the eyes, frequently attended with a high fever, and sometimes terminates in the loss of sight, always gives great pain, and continues for a length of time in most cases. The preparation and application of this remedy is as follows: Having procured a sufficient quantity of the roots, wash them clean and suffer them to dry in the shade, break them with the fingers as fine as you can conveniently, put them in a glass vessel, taking care to fill it about two-thirds with the broken root, add rain or river water until the vessel is filled, shake it frequently and it will be ready for use in the course of six hours. The water must not be decanted, but remaining with the root is to be frequently applied by wetting a piece of fine linen and touching the eyes gently with it."—Am. Journ. Pharm., 1834, p. 201.

† We have testimony to the fact that in portions of Kentucky hydrastis is the domestic remedy for ordinary forms of sore mouth. The patient simply chews small fragments of the root from time to time. After chewing the root, if the saliva be applied to indolent sores, beneficial results are said to follow.—L.

‡ We have an extensive acquaintance in several sections of Kentucky, and have known of infusions of hydrastis being applied to indolent ulcers as a stimulant, but have never known it used on fresh wounds.

§ It is too true that many of these assertions regarding the uses of a drug are unsupported by a single fact that will bear the light. Empiricism in medicine seems to have been a necessity, for our most valued remedies have been handed down to us by men who scarcely recorded a systematic line of investigation. Indeed, we must go back to the aborigines time and again. It is to be hoped that the day will come when medical men as scientists will unite to demonstrate facts, to glean the grain from the chaff. Then as this or that statement is verified or disproved, we trust that a spirit of charity will prevail for those who were misguided, for these same men will be found to have announced many valuable truths.

We have endeavored in the foregoing pages to give a plain, systematically connected record of the introduction of hydrastis into medicine, and its past uses. Modern investigations have disproved many of the statements of other times, but writers still differ considerably from each other, and there is yet room for investigation. This plant is of such importance as to merit more attention than our brief medical record, and we are pleased to present the following independent papers from leading representatives of the various bodies of practitioners.

THE PHYSIOLOGICAL EFFECTS AND THERAPEUTICAL USES OF HYDRASTIS.—(Written for this publication by Prof. Roberts Bartholow, M. D., LL. D., of the Jefferson Medical College of Philadelphia.)*—But little attention has, heretofore, been given to the physiological actions of hydrastis. It is true Schatz,† Felluer, Slavatsinsky, and some others,‡ have made some studies, but their results differ so widely from those herein detailed that it may be questioned whether they operated with sufficiently good specimens of the drug. The alkaloid hydrastine with which the following experiments were made was sent to me by Prof. J. U. Lloyd, the editor of this journal, who is, I hope I may be permitted to say, unimpeachable authority. As hydrastine is quite insoluble, a solution of the hydrochlorate was prepared for me by Messrs. John Wyeth & Bro., which contained 33 per cent. of the salt. The effects of the alkaloid were compared with those of the fluid extract. As the actions of hydrastis consist of the sum of the effects of its active constituents, it is necessary to know how far each contributes to the results. It was soon ascertained that the alkaloid hydrastine is the true active principle—for the very characteristic effects of this were simply repeated by sufficient doses of the fluid extract. The latter is, as might be expected, slower in action, but in respect to the manner of action there was between them no appreciable difference. Three grains of the hydrochlorate caused the death of a frog in four minutes, whilst forty minims of the fluid extract proved fatal in twelve minutes, the mode and character of the action being the same. The results in rabbits were corresponding. In general terms, the effects of hydrastis are those of hydrastine in both classes of animals, but minute differences may hereafter be detected on closer examination.

General Effects of Hydrastine Hydrochlorate in Cold-Blooded Animals.—When ten minims of the 33 per cent. solution are injected into the abdominal cavity of a frog, the following phenomena ensue: In two minutes, muscular rigidity is manifest, with extension of the limbs and inability to move; in three minutes the cutaneous reflex is so heightened that the gentlest tap on the skin causes a tonic convulsion from above downwards; successive tonic convulsions then ensue, with fibrillary trembling between, until at the end of

* Dr. Bartholow desires to acknowledge his indebtedness to Dr. A. B. Brubaker, Demonstrator of Physiology in the Jefferson Medical College, for valuable assistance in conducting the experiments.

† Centralblatt für gesammte Therapie, Band 2, p. 82.

‡ Meditz. Horz. No. 16, 1884. Quoted from the London Med. Record for November 15, 1884.

four minutes death occurs in a strong tetanus. On opening the chest, the heart is still found in action, but in a few minutes more ceases in diastole, all the cavities being full of blood, and its muscular tissue is found to be irresponsive to electrical irritation.

In a rabbit weighing about fifty ounces, forty minims of the same solution, or thirteen grains, caused death in five minutes with the same phenomena—that is, with successive tetanic convulsions, the head drawn forcibly back, the limbs extended, and the respiration fixed, with increasing cyanosis of the ears and mouth. The heart continues in action after respiration has entirely ceased, and on opening the chest then it is still found in slow movement, the auricles most active and all the cavities distended with blood. The muscular tissue of the heart, does not respond to electrical or mechanical irritation.

It follows from the foregoing that hydrastis belongs to the group of excitomotor agents. It heightens preception, the cutaneous excitability and the reflex functions, and it causes death by tetanic fixation of the respiratory muscles.

Determination of the seat of the actions, whether spinal or peripheral.—A frog weighing about twelve ounces was pithed. After division of the medulla, the whole length of the spinal cord was carefully destroyed. No other injury was done, and very little blood lost. Ten minims of the hydrastine solution were then thrown into the peritoneal cavity. The frog remained perfectly limp and flaccid, and no spasm or convulsion of any kind occurred. The heart, on opening the chest some time after the death of the frog, was no longer in movement, the action having ceased in the diastole, and the cavities, as in other instances, were distended with blood.

The spasms and convulsions caused by hydrastine are, therefore, central or spinal, and not peripheral.

Has hydrastine any effect on the peripheral nerves and muscles?—To ascertain this, the left sciatic nerve was dissected out, isolated and a strong ligature applied around the limb the nerve excluded, thus cutting off the circulation from the parts below. Ten minims of the hydrastine solution were now thrown into the abdominal cavity. The usual effects followed—stiffness, rigidity and spasm of the muscles, general tonic convulsions, and intermediate fibrillary contractions. On stimulating the sciatic of the ligatured limb, contractions, not active, of the gastrocnemius followed; but on direct excitation of the unpoisoned muscles of the calf, they responded readily. In the other, the poisoned limb, feeble contractions of the calf muscles ensued on stimulation of the nerve, and similar contractions took place when these muscles themselves were directly acted on. After a time when the influence of the hydrastine had attained the maximum, and immediately after suspension of respiration, both nerves failed on stimulation to excite muscular contractions, and the poisoned muscles became entirely inexcitable.

The foregoing experiments prove that hydrastine exhausts the irritability of motor nerves and muscles.

Action of Hydrastine Hydrochlorate on the Heart.—A freshly removed frog's heart suspended in the solution, rapidly loses its electric excitability, and in a minute no longer responds to a strong current. Applied to the exposed heart *in situ*, the same effect is produced more slowly, and in five minutes an arrest of the movements takes place in diastole, the cavities being fully distended with blood. The auricles resist the action somewhat longer.

The pneumogastrics being divided, ten minims of the solution are injected into the abdominal cavity. The heart is acted on more slowly, and its excitability to stimulation, electrical and mechanical, although much feebler than the normal, still persists. On excitation of the peripheral end, the heart is rather lazily arrested. In the previous experiments, the heart undisturbed in its anatomical relations, it was found that the excitability of the vagus, just before the cessation of respiration, was entirely destroyed, and at the stoppage of the heart's movements, its muscular irritability was lost.

From these experiments we learn that hydrastine acts both on the inhibitory and motor apparatus, destroying their power of response to excitation, but the former function yields later, or after the latter.

To determine more precisely the nature of the action exerted on the cardiac motor and inhibiting apparatus, the vagus was first paralyzed by atropine, and then the usual dose of hydrastine administered. The increased movement caused by atropine was soon lessened by hydrastine, and the heart, after the cessation of the respiratory movements, was ultimately arrested in the diastole, the cavities fully distended as before described. The effect of the atropine was now exhibited in the preservation of the irritability of the heart muscle. In the experiments before detailed, it was found that hydrastine destroyed the irritability of the heart muscle, but when atropine was administered, the response to mechanical and electrical irritation was retained.

The Action of Hydrastine on the Blood Pressure.—A chloralized rabbit weighing about fifty ounces was used for the purpose. The right carotid artery was connected with the manometer and the revolving cylinder in the usual way. The attached tracing exhibits the effects of hydrastine. Up to the point *a* the pressure was at the normal for a rabbit under the influence of chloral, and then began the effects of the drug. It causes, as the tracing shows, some lowering of the blood pressure. The sudden rise at *b* was due to a convulsion, the quantity of chloral not being sufficient to prevent them entirely.

Antagonism between Hydrastine and Chloral.—The number of experiments has been too small to formulate positive conclusions, but enough has been learned to indicate that chloral antagonizes to a large extent the increased reflex excitability and the tonic convulsions caused by hydrastine. It is probable, indeed, that the antagonism will be found as extensive in range as between chloral and strychnine. Thus far I have not had the opportunity to ascertain the lethal dose of hydrastine. Until that is determined, the power

of its physiological antagonists can not be measured with accuracy. Further experiments are making on this point, and will be announced hereafter.

Strychnine and Hydrastine.—A remarkable correspondence can be traced between the actions of strychnine and hydrastine, but the power of the former seems to be the greater, whilst in extent of action the latter seems far more. Both exalt the reflex function of the cord; both induce tetanic convulsions, and both cause death by arrest of the respiratory movements in a tonic spasm. Hydrastine more affects the peripheral nerves and muscles, and to a much greater extent impairs the contractility of the cardiac muscle.

The Therapeutical Applications of Hydrastis.—As the results obtained from the administration of hydrastis constitute the sum of the actions of its several constituents, it may be best to consider the powers of the active principles separately, before treating of the effects of the drug as a whole.

The plants containing berberine are, as a rule, members of the tonic and reconstituant group. Hydrastine being peculiar to hydrastis, much of the effect produced by this agent must be due to the presence of this principle. Prescribed alone, hydrastine has been supposed to have the effects of a tonic, antiperiodic, and to some extent alterant—a term used to signify the power to promote the waste and excretion of morbid materials. The physiological study of hydrastine, as made by Schatz, Fellner, Slavatsky, and others,* has not contributed to the subject of its therapeutical power, although it forms a groundwork for the therapy of the future. If, however, the physiological actions as detailed in this paper be confirmed by subsequent researches, quite a new phase will be given to its therapeutical applications.

As the fluid extract contains all the constituents of hydrastis, it is the most concentrated form available for administration and, therefore, will be the best preparation for procuring the effects of the remedy as a whole, whether given by the stomach or applied externally.

Hydrastis in Gastro-Intestinal Disorders.—As a stomachic tonic, when the condition of the stomach is that of debility, as we find it in atonic dyspepsia, so-called, and in convalescence from acute diseases, hydrastis serves a useful purpose. In common with the bitters, it stimulates appetite and increases the secretion of the gastric glands. Disposing thus of an increased supply of aliment, the constructive metamorphosis is promoted. For this purpose, it is best to administer ten to twenty drops of the fluid extract a few minutes before meals.

Both the alkaloids of hydrastis, exerting an inhibitory influence on fermentation, the fluid extract can be given with excellent effects in cases of catarrh of the stomach accompanied with fermentative changes in certain foods, whether or no, the *Sarcina Ventriculi* be present. The result of the action will be more permanent than the above remark implies, seeing that this remedy can modify, if not remove, that alteration of the mucous membrane

* Centralblatt für die gesammte Therapie, Band 2, p. 82, and Meditz. Obozr. No. 16, 1884. The latter, quoted by London Med. Record, Nov. 15, 1884.

which is accompanied by an outpouring of pathological mucus. To effect this purpose it were better to administer the fluid extract, two or three hours after meals, and the dose should range from fifteen to thirty minims.

As a tonic and reconstituent in the classes of cases above mentioned, quinine is now largely used: it is quite certain that hydrastis can be substituted for the most part with advantage.

The experiments of Rutherford* have confirmed the belief, founded on empirical observations, that hydrastis is an hepatic stimulant, although not one of the most active. As he operated with "hydrastin" so-called, which consists for the most part of berberine, it is probable that the results which he obtained are not equalled by those produced by the exhibition of the fluid extract. Hydrastis has been found useful in gastro-duodenal catarrh, associated with catarrh of the bile ducts—a morbid condition in which the output of bile is lessened by the mechanical obstruction, and the intestinal digestion is impaired in consequence of the insufficient supply of bile, the fermentative changes set up by the mucus which plays the part of a ferment, and the consequent absorption of imperfectly prepared materials. In this state of things we find the true explanation of some cases of jaundice, of most cases of "biliousness," and the initial changes of lithaemia.

The gastro-duodenal catarrh of chronic alcoholism is a condition in which the use of hydrastis has a decidedly beneficial effect, and the improvement in the digestion has seemed to lessen the appetite for alcoholic stimulants. This statement, made by several observers,† has been rather sarcastically commented on by the authors of the National Dispensary,‡ who are, however, pessimistic if not nihilistic in their therapeutical conceptions. The new facts, demonstrating the effects of hydrastine as a spinal stimulant, are additional reasons for supposing it to be possessed of the powers claimed.

For the relief of the intestinal troubles above mentioned, the fluid extract of hydrastis should be given in the interval between the meals, and the dose should be larger (3ss—3i) than in the case of the corresponding stomachal troubles.

As an antipyretic and antiperiodic, the alkaloid—hydrastine—has had no adequate clinical study. Twelve years ago, I made some experimental trials at the Hospital of the Good Samaritan, in Cincinnati, in seven cases of tertian intermittent. White hydrastine in crystals was furnished me by Prof. E. S. Wayne, M. D., of Cincinnati, the well-known chemist and pharmacologist. Two of the cases were recent, uncomplicated, and but a few paroxysms had occurred. Twenty grains of hydrastine, administered in three doses, in anticipation of the seizure, merely modified its violence, but did not prevent it in either case. The second attempt proved successful. Three of the cases more chronic in character required sixty, sixty-five and eighty grains respect-

* The British Medical Journal, 1879, Vols. I. and II. Report of the Committee of the British Med. Association, etc.

† The Practitioner, London, Vol. XVI., p. 121, *et seq.*

‡ Third edition, p. 798.

ively. The two remaining proved still more rebellious, and the patients becoming uneasy, I was forced to resort to quinine. The supply of pure hydrastine was not sufficient to carry on further experiments, and a suitable opportunity to resume the investigation not occurring, I have no further clinical experience in this direction to report.* Nevertheless, these trials, whilst not numerous, are at least significant. They indicate the possession of real antiperiodic power, inferior to quinine, it is true, but apparently inferior only to the great antiperiodic. Since that time, the chemist's skill has produced by synthesis various products approaching in composition closely to quinine, and possessed of powers very similar but still inferior. It may be that under these circumstances, hydrastine will never rival quinine or its analogues, but the powers which it is now shown to possess may require a different statement hereafter.

Topical Applications.—For local use, the best mode of applying hydrastis is in the form of the fluid extract, which may be employed undiluted or diluted with glycerine. Its staining power is an objection, since the color which it imparts to cotton cloth, if not permanent, is at least not readily washed out.

The fluid extract of hydrastis is an excellent topical application in cases of catarrhal inflammation of the mucous membranes. In nasal, faucial, urethral and vaginal catarrh, and in otorrhœa and conjunctivitis, there can be no doubt of its good effects. It may be applied freely in the undiluted state without fear of injury, if no good be accomplished by it. It has proved to be a very efficient injection in gonorrhœa, more especially after the acuter symptoms have subsided. For this purpose it may be diluted with glycerine or mucilage, or both, to the required extent. Formerly when I used to see these cases in considerable numbers, I found it a capital application in cervicitis. I had, also, excellent results in such cases, and in gonorrhœa, from "hydrastine" suspended in mucilage.

To express a final judgment as to its therapeutical value, my conviction is that hydrastis is a useful remedy, and well deserves a trial in the various conditions in which it is recommended above.

THE HOMŒOPATHIC USES OF HYDRASTIS CANADENSIS.—(Written for this publication by Edwin M. Hale, M. D., Emeritus Professor of Materia Medica and Therapeutics in the Chicago Homœopathic College.)—This indigenous drug, first introduced into our school by myself in 1856, has since obtained a great popularity. Many provings and physiological experiments have been made with it, which, combined with an extensive clinical experience, have pretty clearly defined its sphere of action and its place in homœopathic therapeutics.

*The remarkable activity of the pure hydrastine furnished me by Prof. Lloyd, necessitates caution in its administration, until its lethal power in man can be determined. It is now evident that the hydrastine used by me formerly in the treatment of diseases was not pure. I must therefore caution my readers in respect to the administration of the pure alkaloid, and especially its salts, and warn them not to employ this active agent, as they have heretofore been giving berberine, or a mixture of hydrastine and berberine.

Its sphere of action, although not wide, is yet very important. It appears to me to have a decided and specific affinity for

(1) The mucous surfaces—especially those with which it may come in contact.

(2) The mucous glandular system.

(3) The nutritive system.

(4) The circulatory system.

Action on the Mucous Surfaces.—The natural secretion is at first increased; then it becomes abnormal in quantity and quality. At first clear, white, tenacious and transparent, it becomes yellow, thick, green and even bloody, but always tenacious, capable of being drawn out in long strings. In this respect it resembles the mucus discharge caused by *kali bichromicum*, *ammonii bromidum* and *cubebis*. It differs from the mucus flux of *stannum*, *copaiva* and *ammonii chloridum*, which is thick, lumpy and falls in masses. This primary mucous flux of *hydrastis* may pass on to erosion, muco-purulent discharge and ulceration. It probably causes this condition by inducing a primary capillary hyperæmia; next a passive stasis, together with a stimulation of the mucous glands. Finally, from exhaustion or atrophy, the sources of the secretion are cut off, and the mucous membrane becomes dry, glazed, ulcerated and its functions destroyed. Pathologically, this disease of the mucous membranes may be called catarrh, or blenorrhœa. Other medicines cause similar conditions when taken internally, not only in the mucous surfaces with which they come in contact, but through which they may be eliminated (*copaiva*, *kali iodidum*, *cubebis*, *grindelia*, etc.); but we have as yet no proof that *hydrastis* is eliminated through any mucous surface, such as the bronchii, urinary or generative tract. If it acts on these surfaces at all when taken internally, it must act on them by disturbing the circulation in the capillaries. I have never been able to cure blenorrhœas of the above named surfaces by its internal administration, unless it was used at the same time topically; but I do not mean to dispute its ability to do so. Certain it is that we get the best curative effects when it is locally applied to diseased mucous membranes. We have used it successfully in mucous conjunctivitis; otorrhœa; diseases of the eustachian tubes; catarrh of the nasal passages, pharynx, fauces, stomach, intestines, part of the gall duct, urethra, vagina, uterus (leucorrhœa, gonorrhœa, etc.). These catarrhal affections may be simple, or severe, and may extend to erosions or ulceration. If they begin in simple blenorrhœa, they are all amenable to the curative action of *hydrastis*.

Method of Application.—When topically applied we use the tincture, or the muriate of *hydrastine*. The so-called “liquid *hydrastis*” is probably the best preparation. The infusion of the powdered root, when strained or filtered, is very efficacious. The strength of the lotion should vary according to the nature of the disorder, and the amount of the irritability of the surface. When the mucous membrane is red and irritable, a few drops of the tincture, or “liquid *hydrastis*,” or gr.i of the muriate, to the ounce of water is sufficient.

In chronic or torpid conditions the strength may be increased to $\mathfrak{z}$ i of the fluid preparations, or gr.v of the muriate, to $\mathfrak{z}$ i of water. It may be applied with a syringe, atomizer, or as a simple wash, or on bougies (in urethra or uterus), or with a brush (in pharyngitis or conjunctivitis).

Action on the Skin.—The skin being analogous to mucous membrane, it has been supposed that a drug which acts on the one would act similarly on the other. One of our provers records that it caused an erysipelatous rash on the face, neck, hands and fingers, with great heat and irritation, which continued for six days, when the skin exfoliated; others that it caused pustular eruptions. Now the cutaneous analogues of a mucous catarrh, are erythema, moist eruptions, eczema, and even ulcers. In domestic as well as homœopathic practice it has been used successfully in similar skin affections. We have recorded cures of lupus, psoriasis, excoriations, rhagades, ulcers, boils, and even variola.

It was once highly praised as a remedy for cancer, but I can not find any authentic reports of its successful use when used alone. It was generally mixed with chloride of zinc, or some other escharotic.

Action on the Nutritive System.—The Eclectics have always believed hydrastis to be a general tonic. Our experiments seem to show that it acts similarly to cinchona, columbo, gentian, berberis, and others of that class. When given in medicinal doses of the crude drug, it seems to increase the general tone of the organs of nutrition and assimilation. The appetite is increased, digestion is more vigorous, and the bodily weight and strength increases. But if the drug is continued too long, the improvement ceases, and retrograde processes set in. A gastro-intestinal catarrh obtains, digestion fails, assimilation is deficient, constipation and hepatic torpor are present. All tonics, even iron, act similarly when the doses are too large or are continued too long. In these facts we see that hydrastis and its analogues are homœopathic to debility, atony, retrograde metamorphosis, and that the drug should be used in small (not infinitesimal) doses, and not continued too long even in small doses.

It is curative in all disorders depending on the above conditions: namely, generally impoverished blood, emaciation, stomatitis, dyspepsia, indigestion either in the stomach or intestines, biliousness, constipation, etc. The action of hydrastine on the liver was established by the experiments of Rutherford, who calls it "a hepatic stimulant of considerable power, and but a feeble intestinal stimulant." He refers to its purgative power. Hydrastis is not a purgative in any sense. It may cause during its first effects some looseness of the bowels, owing to the increase of mucus, but as the catarrh increases the intestines become sluggish, obstructed and very constipated. English Homœopaths value it more highly than do those of America as a remedy in hepatic torpor and constipation. They find it very useful for hæmorrhoids, congestion of the liver and portal system, sallow, dirty skin, and jaundice. I have found it useful for "mucous piles," as well as "bleeding piles." In

large doses it first causes acute hyperæmia of the liver, but this is followed by passive venous stasis of that organ and of the whole portal system.

On the lymphatic glandular system its action is not yet proven. I doubt if it has any.

Action on the Muscular System.—Hydrastis acts as a tonic. I do not think this acts through the nervous system, as does nux vomica, but through the blood. The increased assimilation of well-digested food allows the muscles to be better fed and better nourished. If the theory of Prof. Schatz, hereafter referred to, be true—that hydrastis acts directly on the muscular coats of the blood-vessels, contracting them—why should it not act on each and every muscular fibre in the body? Not, perhaps, to contract them, but by imparting a peculiar form of tonicity.

But in whatever way it may act, it has been the observation of all practitioners who have used hydrastis, and particularly the muriate of hydrastine (salt of white alkaloid), that the first signs of improvement mentioned by patients is the increase of muscular strength and powers of endurance, and this, too, in chronic, incurable diseases.

While I believe hydrastis to be a powerful tonic and restorative, I am obliged to deny it any specific anti-periodic (anti-malarial) properties. I tested it thoroughly during a practice of fifteen years in a malarious district. It is not and can never be a rival or substitute for cinchona. The practical physician knows that all bitter tonics have some reputation in ague, *e. g.*, chelone, ostrya, euonymus, and others; but they are not anti-malarial medicines. They may be, and doubtless are, capable of removing the malarial cachexia, in which the recuperative forces of the system are too feeble to resist the habit of recurring paroxysms, which are not true ague paroxysms. All these bitter tonics, particularly hydrastis and its active principles, berberine and hydrastine, have the power of restoring the vital forces sufficient to overcome this habit. In this respect hydrastis is more than a rival of cinchona (which is worse than useless in the cachexia)—it is a most valuable substitute. In all cachexias hydrastis is an indispensable remedy. Even in anæmia and chlorosis, it greatly aids iron in restoring the integrity of the blood.

In the debility after wasting diseases, fevers—typhoid or gastric; after losses of blood, or due to depressing emotions, also in neurasthenia, the hydrastia berberine phosphate or hypophosphite have done me excellent service. We have found it very useful in gall-stones, not so much for the colic caused by their passage as to remove the tendency to their formation. It may dissolve the biliary concretions by causing a flow of thinner bile, or aid in their expulsion by removing (as in jaundice) the catarrh of the gall duct. Several German Homœopathists have reported cases of tumors of the stomach and pylorus which disappeared under the careful and protracted use of hydrastis.

It is a curious fact in the history of our indigenous remedies that just about the time we think we understand all their qualities, and know all their uses, some foreign physician discovers new qualities and new uses for them.

This is partly true of hydrastis. I have recently read a lecture delivered before the Gynæcological Section of the Congress of German Philosophers and Physicians, held at Freiburg, in 1883, by Prof. Schatz, of Rostock, Germany. He gives as a result of his investigations that "hydrastis acts on the mucous membranes by contracting the vascular system."

But such a condition must be due to its action in large doses, and must be followed by its secondary effects, which would be of an opposite character, namely: passive congestion of these tissues. This action can not, however, account fully for its blenorrhagic effects. It must have some other action, especially when locally applied, and this action I am sure is that of an irritant to the glands of the mucous membranes. It probably has, in crude quantities, a double and simultaneous primary action, namely: contraction of the vascular supply, and irritation of the glandular supply. This vascular tension will after a time be followed by vascular relaxation; and the acute primary blenorrhagia by a chronic blenorrhœa with tissue paresis.

Further, Prof. Schatz says that "in many particulars, hydrastis and ergot are not unlike, but not infrequently hydrastis is efficient in cases of hæmorrhage where ergot is powerless, or even of positive injury, as also in some cases of myoma. It appears to me that we can attribute the action of hydrastis to the contraction, pure and simple, of the blood-vessel-wall, thereby lessening the congestion of the genital organs, while ergot spends its action on the muscular fibres of the uterus." "In the non-gravid uterus," he says, "the continuous administration of hydrastis causes a retardation of the menstrual period, with a diminution of the amount; it causes the pain to be less; even in menorrhagia and dysmenorrhœa of virgins, without any local causes, when pain is absent. Its action in myoma is often quite remarkable. Hæmorrhages caused in this manner diminish very much, or disappear entirely, after the use of hydrastis— even where Bombelin's ergotine has been employed most energetically; I have observed a number of times that where hydrastis had been administered to virgins for menorrhagia, normal menstruation set in, and occasionally the catamenia did not make their appearance for one, two or three months." This result was caused by massive doses. Prof. Schatz gives twenty drops of the fluid extract four times a day, causing, we may presume, the extreme primary effects of the drug. He does not give a differential comparison of the effects of hydrastis and ergot, which would be of great value and interest, but he admits, or implies, that he is not yet able to make such a comparison.

The best authorities describe the action of ergot to be as follows: "The action of the heart becomes slower, and an enormous rise takes place in the blood-pressure. This influence on the circulatory system modern research has shown to be due to the action of ergot on the vaso-motor system; it increases the action of this system, and causes a contraction of the arterioles."

Again, it is said to diminish the blood-supply to the cerebro-spinal axis, to the vegetative organs, the skin and muscular system. It is therefore diffi-

cult to explain the difference in the action of the two drugs, unless we suppose that hydrastis acts directly on the blood-vessel walls and not through the vaso-motor centers. But we doubt if this can be the case. There are many symptoms of hydrastis, in our meager provings of it, which indicate that it also diminishes the blood-supply of the brain—as witness the “tinnitus aurium, vertigo, dimness of vision, roaring in the head, with dull headache; a ‘narcotized’ feeling in the brain, feeling as if intoxicated; terrible headache and vertigo, horrible dreams.”—Hale’s New Remedies, third edition.

It is possible that a more heroic series of provings would evolve more vaso-motor symptoms, but when we consider the large quantities, continued for a long time, used in Eclectic and domestic practice, such a supposition does not seem probable.

But, while its full and true action is yet unexplained, we may take advantage of clinical experience to teach us the action of the drug and its value in certain diseases.

Prof. Schatz, in his memorable lecture, fortifies his statements by the narration of six cases of fibroid tumors of the uterus (myoma), in which he used hydrastis successfully in controlling and curing the hæmorrhages, but he does not say what became of the tumors. We know that not all cases of uterine fibroids are attended by hæmorrhage. If hydrastis acts by diminishing the vascular supply, it ought to arrest the growth of the myoma, or other non-malignant tumors. Now this brings us back to the alleged curative power of hydrastis in cancer. I have carefully examined all the records of our school relating to the use of hydrastis in tumors and cancer, and I can not find a single case where it entirely removed a cancer, or scirrous growth, before or after the stage of ulceration. But there are cases reported where hard, movable tumors appearing in the breast, stomach and uterus, have decreased in size, or disappeared altogether, after the internal and topical use of hydrastis.

It is my belief, based on a large personal experience and observation, that all the tumors benefited by this drug were fibroid in character, and the result was brought about, not by any “absorbent” action, but by diminishing the supply of blood, and thus cutting off the nutrition of the growth.

Ergot has certainly arrested and diminished the growth of myoma in the uterus, but we do not know that it has acted as well in fibroid tumors elsewhere.

Strychnine has the same action as ergot on the muscular structure of the uterus; so has caulophyllum, cimicifuga, and other drugs, but we do not hear of them as being of value in fibroid and other growths in the uterus.

Hamamelis, trillium, turpentine, phoradendron, millefoil, and others, act as well as ergot in controlling hæmorrhages, but we do not know them to be useful in any kind of tumor.

These are mysteries of drug action which yet remain unsolved.

It would appear from the foregoing that if the *modus operandi* of hydrastis

is as stated, its analogues are viburnum, ammonium bromide, ammonium chloride, and a few others.

Viburnum arrests and prevents the pain of dysmenorrhœa and hæmorrhages. It is supposed to act on the motor nerves of the uterus, relaxing contractions of muscular tissue. If so, it must act opposite to ergot. How, then, does it arrest hæmorrhage? It would seem that it could not affect the coats of the blood-vessels in a manner opposite to its action on the muscles.

Here is an anomaly which can only be explained by accepting the theory advanced by some Scotch obstetrician, that hæmorrhage from the uterus often arises from undue contraction of the muscles of that organ.

The bromide of ammonium has been found curative in ovarian and uterine tumors. It is capable of arresting hæmorrhage, and acts on the muscular structure of the uterus and its vessels similarly to hydrastis.

Muriate of ammonium has the same specific action on morbid growths, but is not known to arrest uterine hæmorrhage.

The action of hydrastis on the uterus may be said to be unique; it has no close analogue. It is not alone in hæmorrhage from uterine fibroids or myoma that hydrastis is useful. Prof. Schatz reports one case of congestive dysmenorrhœa; six cases of hæmorrhage in virgins, where the bleeding continued after the use of the curette; three cases due to parametritis, cicatrices and contractions; two from incomplete involution of the puerperal uterus; three cases from endometritis and metritis; and five cases of climacteric hæmorrhage. In all these cases various other means, drugs and operations had been used, and failed, but hydrastis performed a cure.

Dr. Schatz warns us to use the proper dose. Too small doses have no action; too large too much effect. The quantity he found generally useful was 20 gtts of the tincture three times a day.

I mention this because the illogical custom of many of our school is to select the dose in accordance with some arbitrary notion or preconceived theory. It is absurd to prescribe ergot in a middle or high attenuation for non-tractility of the uterus; and it would be just as absurd to give 20 gtts of the crude in uterine spasms. The dosage in these cases must be reversed, or it is not curative.

By Dr. Schatz's observations we learn that the sphere of curative action of hydrastis, already wider than we supposed, bids fair to become more and more enlarged, especially in the direction of its action on the circulatory system. If hydrastis increases the tonicity of the muscular fibres of the terminal blood-vessels, it must also increase that of the large arterial and venous trunks, and even of the heart itself. And if it does this without acting on the vaso-motor centers, it must prove far more valuable than ergot, for its effects must be more lasting. It follows that it may prove to be one of the chief remedies, if not *the* remedy, for chronic congestion, or more properly, stasis of the various organs of the body. It may prove to be to the arteries what hamamelis is to the veins, or it may rival the latter in its own

sphere of usefulness. Further experiments and clinical observations are needed to substantiate this theory, but I can safely say that it is my conviction, based on many years' experience in its use, that it is of veritable value in chronic blood stasis in the liver, spleen, uterus, abdomen and portal system. I believe too that I have seen proofs of its value in passive stasis of the brain and lungs, for within the last year or two I have observed excellent results from the use of the hypophosphite of hydrastine in affections of the latter organs. I am sure I have seen its good effects in weakness of the muscular structure of the heart, with tendency to dilatation. It seems to build up the muscular tissue, while digitalis or convalaria regulates the rhythm.

I will close this paper by giving an excellent pen picture of the gastrointestinal troubles, for which hydrastis is specific. It is copied from an article written by Dr. Clifton, of Northampton, England:

"*The Facial Expression* is dull, heavy, of a yellowish white color, sodden looking, not unlike that in which mercurius is indicated, but whiter, and having less animation. Though there is in its provings no reference to the expression or complexion, as affording reasons for selecting hydrastis, I have frequently found that when the gastric symptoms calling for this medicine have been present, the character of the face has been as I have described.

"*The Tongue* is large, flabby and slimy-looking. Underneath the fur the tongue is of a bluish white color, having in its edges the imprints of the teeth. So far it is like the mercurius tongue, but lacks the tremulous character of this organ, so often seen in cases benefited by mercurius. The coating is of a yellow, slimy, sticky fur.

"There are morbid states occurring in other organs, to which hydrastis is Homœopathic, but where the appearances of the face and tongue I have described are not present. In the dyspepsia it relieves. Both are met with.

"*The Eructations* are generally sour or putrid, more commonly the former than the latter.

"*The Appetite* is generally bad; the power of digesting bread and vegetables being especially weak. Both are followed by eructations.

"*The Stomach* has a sensation of weight (not as after nux and bryonia, 'weight like a stone'), and with the weight and fullness, an empty, aching, 'gone' feeling, more or less constant, but aggravated by taking a meal. The aching, 'gone' feeling is something like that produced by gelsemium, but is attended by more general fullness of the stomach, and more sour eructations. Further, although the gelsemium tongue is sometimes coated white or yellow, it is not so large and flabby as is the hydrastis tongue. This symptom is, I am aware, produced by many other medicines besides gelsemium, especially by ignatia and cimicifuga, but ignatia and cimicifuga do not give rise to the other symptoms peculiar to hydrastis. In tea-drinkers this symptom occurs frequently, but with them the tongue is generally white (except when colored by the tea), and in their dyspepsia cinchona is often found

to answer better than other medicines, especially in removing the flatulence with which they are commonly troubled.

"*The Action of the Bowels* may be either infrequent and constipated, or frequent, with the stools loose, soft, light colored, and with flatus. But as a rule the bowels are constipated, and stools lumpy and covered with slimy mucus, in cases indicating hydrastis."

THE USES OF HYDRASTIS IN THE ECLECTIC SCHOOL.—(Written for this publication by Prof. John M. Scudder, M. D., Professor of the Practice of Medicine in the Eclectic Medical Institute, Cincinnati.)—In some respects the hydrastis has been much over-estimated. It has been recommended as an antiperiodic, but it has but a feeble influence either as a prophylactic or a remedy opposed to malarial disease. It has been recommended as one of the best if not the best of bitter "tonics"—meaning a remedy to increase the appetite, digestion, blood-making and nutrition. But in this it is much overrated, and will not give satisfaction unless a special pathological condition exists.

This brings us to the consideration of the indications for its use, and its contra-indications. It is a remedy in atony of mucous tissues, with increased secretion; it is a remedy in irritation or inflammation of mucous tissues if secretion is free, whether it be mucus or pus. In this case it is a tonic, and improves nutrition, giving a better circulation and innervation. It has been claimed that it relieves irritation and gives tone to the parts, and with the conditions named this is a fact.

In catarrhal gastritis it is tonic and peptic, as it is in intestinal catarrh or catarrhal dyspepsia. It is a good remedy in stomatitis with increased secretion, in acute or chronic pharyngitis, and in some cases of nasal catarrh.

A solution of the soluble salts has proven very useful as an injection in the second stage of gonorrhœa, and in gleet. It is an excellent remedy in disease of the cervix uteri, and in cervical metritis, with profuse secretion from the cervical canal. In these cases the application should be thorough. In ulceration of the rectum it will sometimes prove a most efficient remedy.

In the second stage of purulent conjunctivitis a solution of these salts will give good results, and in some cases of chronic conjunctivitis the effect will be beneficial.

The salts of berberine (sulphate or phosphate), as well as the alkaloid itself are very convenient for dispensing, especially when the physician carries his own medicine. One to four grains to a half glass (℥iv) of water makes an excellent bitter, and with three or four drops of tincture of nux vomica, a good peptic. A collyrium or an injection for the purposes named is as readily prepared.

One use of hydrastis is yet to be named. In some cases of cancer with sloughing of tissues, and in malignant ulceration, no application will do more to retard the progress of the disease than an infusion of the crude article or a solution of the alkaloid. It has been claimed that the internal administration of the remedy will prove curative. I am satisfied that in some cases this use

of hydrastis will do much to relieve pain and to lengthen life even if it does not prove curative.

THE USES OF HYDRASTIS CANADENSIS IN THE ECLECTIC SCHOOL.—(Written for this publication by Prof. John King, M. D., Professor of Obstetrics and Diseases of Women, in the Eclectic Medical Institute, Cincinnati). While as a general vegetable tonic, hydrastis is inferior to certain other bitter tonics, as, gentian, colombo, etc., it will be found superior to them in the treatment of subacute and chronic inflammation of mucous membranes, upon which it exerts a peculiar tonic and slightly astringent effect, whether taken internally, or applied locally. In the majority of cases, its local application is followed by more prompt and positive action than its internal administration. Whether its power of contracting vessels be owing to a tannic acid, or to a principle similar to that in ergot which causes a like effect, has yet to be determined.* Administered internally, it has proved efficacious as a tonic, in enfeebled conditions of the alimentary canal with infants and children; in restoring tone to the intestinal mucous coat after severe attacks of diarrhea, dysentery, and other debilitating maladies; and in removing the indigestion, and restoring the appetite in those cases of indigestion and anorexia of adults due to an abnormal condition of the mucous coat of the stomach. As a local application it has proved valuable in conjunctivitis, in ulcerations of the mouth and fauces, in vaginal and uterine leucorrhea, and in all cases of enfeebled mucous tissues. In the chronic forms of cervical and corporeal endometritis, it has acted with success, being applied in the form of powder, made by evaporation of a decoction of the root, rubbed up with simple cerate or vaseline, and introduced into the uterine cavity by means of a tube made for such a purpose. In combination with other agents, it exerts beneficial influences that can not be had by the employment of either of the articles separately. Thus, a strong decoction of the root, to which has been added one-third or one-fourth its volume of tincture of capsicum forms a successful application to corneal ulcerations, and to all atonic ulcerations of mucous tissues. In ulceration of the bladder, the decoction mixed with an equal volume of decoction of geranium, and injected into the bladder, has effected cures even in cases where all previous treatment had failed. This same decoction has never failed me yet, as a local application in ophthalmia neonatorum. The decoction, employed in combination with decoction of caulophyllum, has been found efficacious in thrush, and aphthæ of infants and children. Berberine, or muriate of berberin, does not appear to possess the positive action upon abnormal mucous tissues that is manifested by the root in decoction, fluid extracts, or a powder made by evaporating the decoction to dryness."

The preceding statement was written some four or five months ago, and placed in the hands of Prof J. U. Lloyd. To my great pleasure and surprise I have just noticed that in the section of Gynæcology in the Congress of naturalists and German physicians, held at Fribourg, in Brigau, Dr. Schatz, of

* Do not confound this with the yellow alkaloid berberine.

Rostock, invited the attention of his colleagues to the American *Hydrastis Canadensis*, the therapeutical effects of which rather astonished him. He found this agent efficacious in hemorrhages from myoma, from congestive dysmenorrhea, from subinvolution, also in those attending metritis and endometritis, as well as those occurring at the period of the menopause. He supposes the medicine acts upon the uterine mucous membrane, exciting vascular contractions, through which mechanism it diminishes congestion of the genital organs, thus acting very differently from ergot, the influence of which is exerted upon the uterine muscular tissue.*

REMARKS.—The foregoing independent papers on the therapy of hydrastis and its products, will be of general interest to the medical profession of America. To us, one feature is unexpected, namely, the announcement of Prof. Bartholow that “the alkaloid hydrastine† is the true active principle.”

The physiological action of hydrochlorate of hydrastine as demonstrated by Prof. Bartholow is such as to warrant a close clinical study of this salt, which has been heretofore generally neglected. The negative results that followed the investigations of early experimentors, were doubtless owing to the use of the insoluble alkaloid, or impure hydrastine, for the active nature of the salt, as shown by the investigations of Prof. Bartholow, would lead us to infer that the popularity of hydrastis and its pharmaceutival preparations is largely owing to a natural salt of hydrastine, modified, perhaps, by the berberine with which it is intimately associated, rather than the reverse. In the plant, this alkaloid, and berberine exist in the form of very soluble salts, and the long accepted uses of hydrastis in diseases of mucous surfaces, instead of as a mere tonic, like other berberine yielding plants, would alone indicate that berberine is not the prime factor. Indeed, it has long been known that solutions of berberine were not, in eye diseases of the value of infusion of hydrastis. This has always been accepted by Prof. King. This new light would lead to the opinion that the estimation of the value of hydrastis by our berberine process was fallacious, and that we should rather estimate the hydrastine of the drug.

Acting, therefore, on the information conveyed by Prof. Bartholow, we placed the hydrochlorate of hydrastine in the hands of several acknowledged authorities of the medical profession, and as a result we are enabled to present the following clinical contributions. It will be noticed that Prof. Sattler, having examined both berberine and hydrastine, also reports that hydrastine is the active agent.

THE PHYSIOLOGICAL EFFECTS AND THERAPEUTIC USES OF BERBERINE AND HYDRASTINE IN OPHTHALMIC AND AURAL PRACTICE.—(Written for this publication by Prof. Robert Sattler, M. D., Ophthalmic Surgeon to the Cincinnati Hospital, etc).—The want of a satisfactory preparation of *Hydrastis Canadensis*, perfectly soluble and free from the well-known objectionable features of

* The balance of this statement as to the form employed, doses, etc., of this medicine, are so nearly similar to those related by Dr. Hale, that we have with Dr. King's consent, omitted them, and refer our readers to the article by Dr. Hale, for further information concerning Dr. Schatz's investigations.—Ed.

† Do not confound this with the yellow alkaloid berberine.

the drug, has until recently prevented its more general and extensive use and application in the management of the various catarrhal affections of the eye and ear.

At the request of Prof. J. U. Lloyd, I commenced a series of observations to test the physiological properties and therapeutic uses of two soluble salts of hydrastis, *i. e.*, diberberine sulphate and hydrochlorate of hydrastine, which he kindly furnished me, in powder form and in one, two and four per cent. solutions.

The investigations were conducted at my clinic and the records of the progress and results of the cases in which either remedy was resorted to, were carefully compiled by the clinical assistants, Drs. C. H. Castle and C. R. Holmes.

BERBERINE DISULPHATE.—*Physiological Action.*—Observations were begun with the berberine solutions. Two or three drops of a two per cent. solution dropped into the conjunctival sac caused slight irritation and injection of the palpebral and ocular conjunctiva. The objective and subjective disturbance, however, subsided quickly.

A four per cent. solution excited greater local irritation, more profuse flow of tears and mucous and also more pronounced subjective discomfort. The duration, however, of these symptoms was brief.

Therapeutic Application of Berberine.—To test its efficacy to relieve or modify catarrhal alterations of the conjunctiva (conjunctivitis simplex, acute catarrhal conjunctivitis, etc.), two and four per cent. solutions were resorted to, but in every case the results were negative, or at least, unattended by appreciable good effects, even after prolonged and systematic use.

The principal objection to the disulphate of berberine solution was, not so much the discomfort and irritation it induced, but principally on account of the deep staining (yellow) of the adjacent parts.

The hyperaemia of the conjunctiva, produced by the instillation was too transitory and was not effectual in modifying, after repeated trials, the local symptoms; or in bringing about relief from the scratching and burning sensations produced by the disease. Owing to almost uniformly negative results, additional observations were not made.

If the use of the berberine solutions proved of little or no value in the treatment of catarrhal affections of the eye, the use of both strong solutions and the powder in substance proved absolutely ineffectual when resorted to for the purpose of modifying or arresting catarrhal or purulent discharges from the middle ear.

In the following cases it was applied,—a four per cent. solution dropped into the ear twice a day, after syringing and the insufflation of the powder was resorted to once a day.

Case I. R. H. æt 4. Acute catarrhal otitis media, perforation of membrana tympani, slight discharge. Applied powder and solutions Nov. 2, 3, 4, and 5. The discharge became very profuse during this time, the powder incrustated and caused pain and suffering. Nov. 6, discontinued berberine, and used powdered boric acid, and discharge stopped in two days.

Case II. K. F. æt 16. Chronic otitis media purulenta. First application Oct. 15, continued until Oct. 28. No change of symptoms. Oct. 29, complained of pain in the ear, discharge more profuse. In spite of great care in the introduction of the powder, and the daily cleansing, it underwent incrustation.

Case III. G. B. æt 13, Chronic purulent otitis media. Oct. 26, First application, continued until Nov. 7. No favorable change, incrustation also troublesome.

Case IV. Subacute purulent otitis media. First application Oct. 24. Continued to Nov. 7. In this case there occurred considerable improvement. Incrustation also troublesome.

Case V. Chronic otitis media purulent, was tried for ten days: symptoms became worse.

In a number of other cases the remedy was used, but after several days was abandoned, for the reason that no improvement or change occurred to warrant its continuance.

When resorted to in solution, coagulation or precipitation occurred at once but no pain attended its use. The principal objection to its use in this locality, and this applies particularly to the powder, is, that rapid incrustation, due to chemical transformation from contact with the discharge occurs. The staining of the parts also constituted an objectionable feature. The removal of the incrustated masses from the external canal became necessary, on account of discomfort and pain produced. In some of the cases the removal was tedious, difficult and painful.

HYDRASTINE.—*The Physiological Action and Effects of Instillations of Hydrochlorate of Hydrastine.*—Two or three drops of a two per cent. solution dropped into the conjunctival sac of a healthy eye, causes at once active stimulation of the palpebral and ocular divisions, attended by the usual reflex symptoms—lachrymation, blepharo-spasm, and a pungent and burning pain, which, however, is of short duration, rarely lasting longer than two or three minutes. With the subsidence of the pain, more or less moisture of the eye remains, and a watery mucus secretion often accumulates at the outer and inner canthus. After the expiration of one hour, all evidences of the instillation have disappeared.

A four per cent. solution causes more marked subjective discomfort, more active and persistent hyperæmia of the conjunctival area, more pronounced reflex symptoms, together with increased stimulation of the secretory apparatus. Stronger solutions cause an intensification of all these symptoms, and in addition, probably in consequence of the irritation to the sensory nerves of the cornea, contraction of the pupil. The myosis is most probably the immediate result of the irritation of the superficial sensory nerves of the globe, and is not due to a direct action upon the sensory and muscular structures of the iris.

Cold applications to the lids modify greatly the local symptoms, and also the discomfort attending instillations of weaker solutions; and the application of stronger solutions is greatly mitigated by immediate washing off the conjunctival surfaces with camels hair brush and tepid water. The inferences from a number of trials establishes that in mild solutions, hydrochlorate of hydrastine is a tonic and stimulant to the conjunctiva, increasing for the time

being, its functional activity. It can also be inferred that the remedy exerts its beneficial effects, by its action in arousing and stimulating the functional activity of the complex glandular structures, by the active hyperæmia produced by its instillation. This was corroborated by numerous trials in those cases, in which the remedy was resorted to in variable strength of solution, to accomplish such effects, in diseased states of the conjunctiva, which the instillation into the normal eye rendered probable. It appeared therefore of probable value in those pathological processes of the mucous membrane attended by more or less pronounced passive congestion, relaxation of structure, and altered or suspended functional activity of its glandular apparatus.

In all catarrhal forms of conjunctivitis and in the first or catarrhal stage of more serious lesions, one and two per cent. solutions exerted a beneficial influence on the local symptoms. The secretions appeared less acrid and were reduced in quantity and perhaps altered also in composition; particularly was this observed, if in addition to frequent instillations of weaker solution, an application of a stronger solution five per cent. was made once a day to the conjunctival surfaces of the everted lids, by the aid of a camel's hair brush and the surfaces immediately washed off with water.

In follicular conjunctivitis, an affection quite common among anemic and scrofulous children, and also among adults living amidst unfavorable hygienic surroundings, it was found to possess decided advantages over the customary astringents and local stimulants ordinarily resorted to. The disease is eminently chronic and contagious. In many cases it exists in a latent form and gives rise to little annoyance, or the discomfort is ignored by the patients, until vision is interfered with by the accumulation of mucus and irritation of the lid borders, due to the acrid or irritating character of the discharges. Often it appears in an endemic form in certain localities, and in other instances it affects all the members of one or more families. Lack of cleanliness on the part of the person or persons affected, and the careless use of towels and handkerchiefs by the other members of the family constitute the principal channels of contagion. On account of its chronic course and the general or frequent vitiated state of the constitution of persons affected, it is a most troublesome affection to manage. The use of hydrochlorate of hydrastine solutions in this annoying affection has been particularly satisfactory, and local and subjective symptoms have been effectually modified and the course of this always tedious affection, has been altered and shortened. Compared with other remedies, the subjective discomfort attending its use was less annoying and subsided more rapidly, and the improvement was more lasting.

Therapeutic Application of Hydrochlorate of Hydrastine.—Bearing in mind its local action when instilled into the healthy eye, it was resorted to in a large number of cases in which this action would appear desirable in order to promote, modify, or arrest those local symptoms, which are the common and frequent attendants of acute, subacute and chronic catarrhal, follicular, granular, blennorrhœal, etc., inflammations of the conjunctiva.

In the treatment of chronic catarrhal conjunctivitis, and particularly that variety known as conjunctivitis siccus, it was found of great service. This affection is eminently tedious and annoying, to both physician and patient. Among the most distressing symptoms, is a sensation of dryness and scratching, attended by a feeling of weight and heaviness of the upper lids. A perceptible reduction in the quantity, and also an alteration of the quality of the secretions of the conjunctiva can be observed. In the majority of instances anæmia, physical exhaustion, or other disturbances which depress the general health, are present, and to the local and general symptoms are added, failure of the accommodative power of the eyes and most annoying asthenopic symptoms. In those cases in which an optical error of the eyes co-exists, these symptoms appear in a most pronounced form and defy or effectually prevent all application of the eyes for close work. In the management of this variety of conjunctivitis, ordinarily so troublesome and tedious, hydrochlorate of hydrastine, in 1 and 2 per cent. and even stronger solutions, was found of particular advantage. The favorable influence exerted upon the progress of the disease, and also in modifying the annoying subjective symptoms, was probably assignable to the quick and decided stimulation of the vascular and secretory apparatus of the conjunctiva.

In chronic granular conjunctivitis, it was also found of benefit. In a large number of cases it was resorted to systematically during the second or stage of granular infiltration. In these cases daily applications of a stronger solution (5 per cent.) were made to the everted surfaces of the conjunctiva and immediately washed off with water. Both the use of weak collyria and the topical application of a stronger solution exerted a beneficial local and subjective influence, and effectually modified the protracted course of this most troublesome and chronic affection. In the transition or third stage of the disease, weaker solutions were used, and occasionally an application of a stronger solution. In the treatment of this extremely chronic and intractable affection it was not found to possess advantages over the customary remedies resorted to, and in several cases its use had to be discontinued, on account of the severe reaction and suffering which followed the application. In blepharitis marginalis it was applied in solution (2 per cent.) to the eroded and ulcerated margin of the lid. These cases progressed favorably and the improvement was assignable without doubt to the local stimulating effect of the remedy.

Reviewing briefly the advantages of this remedy in the management of the various diseases of the conjunctiva and its value as a therapeutic agent, it can be stated, that it is of principal advantage in catarrhal conjunctivitis, and especially in the chronic forms. It is of particular benefit in follicular conjunctivitis, and also an efficient remedy in granular conjunctivitis, blepharitis marginalis, etc. It appears to exert its specific local effect by exciting a temporary more or less pronounced hyperæmia of the conjunctiva, and, in consequence, active stimulation of its vascular and secretory structures. The action of hydrochlorate of hydrastine is prompt and decided.

In weak solutions it is a tonic to the mucous membrane ; in stronger solutions a more or less pronounced irritant effect is added, and in still stronger solutions it is a powerful irritant. As a choice of remedy, it deserves attention and preference, in all the various affections of the conjunctiva attended by a disturbance of its functional activity, due to an acute, sub-acute or chronic process of inflammation. On account of its active stimulant properties, it modifies and aids in correcting the secretions and relieves in this way the annoying symptoms and almost invariable concomitants of catarrhal inflammations. It is, therefore, a valuable tonic, stimulant or irritant to the mucous membrane. In those cases where the remedy has not been the first choice it may prove a valuable substitute for other astringents or stimulants, which may have been unsuccessfully resorted to. In other cases it will prove a serviceable agent, occasionally resorted to in conjunction with other remedies.

Hydrochlorate of hydrastine is contra-indicated in all affections of the cornea or iris, either primary or occurring as complications in connection with or the result of conjunctivitis. It is also of no value, and, therefore, contra-indicated in all deep-seated affections of the eye. It is primarily and principally a tonic, stimulant or irritant to the mucous lining of the lids or conjunctiva, and its scope and efficiency of action is limited to functional or structural alterations of this important membrane.

In the ear, the use of solutions of hydrochlorate of hydrastine was also resorted to, but the number of observations was more limited. It was used, to modify or arrest irritating catarrhal and purulent discharges from the external auditory meatus, and its use was attended and followed by the same good, and in some instances even better results, than after instillations of the customary mineral astringents, or iodoform, boric acid, etc. In two cases of acute and five of chronic purulent otitis media the results were carefully noted. After thoroughly syringing the external auditory canal and middle ear, inflation by Politzer's method was practiced. This accomplished, the bottom of the meatus and those parts of the middle ear which were accessible through the perforation of the membrana tympani were carefully cleansed and dried, by means of absorbent cotton attached to a holder, and the powder applied to the eroded and exuberant mucous membrane. (In three out of the five cases this was an easy task, as the membrana tympani had been almost completely destroyed.) The results of systematic applications in these chronic cases were certainly favorable ; in two of the five cases a marked reduction in the quantity and quality of the discharge occurred. All the cases had been under treatment and hydrochlorate of hydrastine solutions were substituted. All were apparently benefited ; the discharge was reduced in quantity and lost its irritant and offensive characteristics. It can safely be said, that in many cases, carefully selected, the remedy is of advantage and deserves a trial either as a substitute or as a first choice. In several cases of granulations and polypoid formations, the result of otitis media purulenta, it was applied in substance, and, although it caused severe pain, it effected by systematic application a disappearance of the exuberant growths.

HYDRASTIS AND HYDRASTINE HYDROCHLORATE IN DISEASES OF THE SKIN.
—(Written for this publication by Dr. John V. Shoemaker, of the Jefferson Medical College of Philadelphia).—Hydrastis is a valuable drug in diseases of the skin, both internally and as a topical application. It is especially useful as a stomachic tonic, and as a hepatic stimulant in cutaneous affections depending upon gastro-intestinal disorders.

It is best administered in the form of the fluid extract of hydrastis which Prof. Roberts Bartholow has shown to contain all the constituents of the drug and is the preferable preparation to use. In *seborrhœa-sicca* or *oleosa*, which frequently develops from some alimentary trouble, the scaly, reddened or greasy state of the skin may lessen or disappear by the use of ten or twenty drops of the fluid extract of hydrastis three times daily. The red or white of papules black points or pustules of acne or the enlargement of the blood vessels and tissue of *acne-rosacea* due to the same cause may alone be relieved or cured by the internal administration of hydrastis. It is an excellent remedy to use in scrofulous diseases of the skin, in patients having feeble digestion, loss of flesh and enlarged glands, with or without unhealthy ulcers. In cases of this nature it will stimulate the appetite, lessen the involvement of the skin and assist the action of local medication in removing the disease. It has also acted in a happy manner upon some cases of lupus, sycosis, boils, carbuncles and ulcers, on which the local condition was largely due to a lack of nutrition of the system. Eczema which is so often depending upon debility or some gastro-intestinal disorder, may at times be greatly relieved or cured by free doses of the fluid extract of hydrastis.

Children suffering with the pustular form of this disease, known as eczema *impetiginodes* or milk crust, small doses of the fluid extract from one to five drops in mucilage or glycerine three times daily increases the digestive power, lessens the formation of pus, and has a powerful tonic action upon the previously enfeebled system. In broken down syphilitic subjects, especially in those in whom the alimentary canal is weak and irritable, often from alcoholic excess, or from the use of too much mercury or one of the iodides, the use of hydrastis is attended with most marked and beneficial results.

Hydrastis may be employed alone internally or in some cases its conjoined internal and external use will at times be found most efficacious. The range of usefulness, however, as a topical application, is even greater than from its internal administration. The fluid extract, which is the preparation generally employed for local use, has both a stimulant and an astringent action on the integument which is well marked when the skin is denuded or inflamed. It may be used undiluted, or what is even better, diluted one-half or one-third with water, oil, mucilage, or glycerine. Inflammatory affections of the mucous membrane, especially stomatitis, syphilitic lesions, and eczema are greatly benefited or even at times removed by the application of the fluid extract of hydrastis. The fissured form of the latter diseases which occurs around the

mucous outlets, as on the lips and about the anus, or on the flexor surfaces and between the fingers and toes are sometimes rapidly improved by its use. It also exerts a most efficacious action or lessens the inflammation and thickening in chronic eczema, whether involving the parts just referred to or other regions. Abrasions, sinuses, ulcers and granulations are greatly improved by the application of this remedy.

While the use of the fluid extract of hydrastis has been attended with much benefit in many of the diseases just cited yet its employment has been open to a very great objection from the staining which follows everything with which it comes in contact. This staining power which is usually imparted to the clothes of patients, is not easily removed even by washing and the unpleasant effect that follows the employment of this drug would almost entirely preclude its adoption in private practice, when so many other, elegant, cleanly and efficacious preparations are now constantly on hand for use. Fortunately, however, the objection referred to has been entirely overcome by the recent investigations of Prof. Bartholow, who has demonstrated the active principle of the drug hydrastine, which can be combined to form hydrastine hydrochlorate, which has all the physiological effect of the former drug. Further, the salt so formed not only possesses all the good qualities for cutaneous application, claimed for hydrastis, but it is also perfectly free from the staining qualities of the latter drug.

Hydrastine Hydrochlorate.—This salt occurs as a fine white powder slightly tinged with yellow, inodorous but very bitter and soluble in water, alcohol, oils and fats. Its color, its odorless character, and its great solubility furnishes a remedy of unusual advantage for topical application in diseases of the skin.

During a short experience with this preparation I have found it most useful mixed with water, alcohol or fat in hyperidrosis, seborrhœa, acne, eczema and in ulcers. Thus from five to twenty grains of hydrastine hydrochlorate to the ounce of alcohol, has a most beneficial effect on excessive secretion which may occur in the axillary or inguinal regions, or on the palmar and plantar surfaces. This same combination acts well in seborrhœa-sicca, especially of the scalp, attended with loss of hair, the stimulant and astringent action of the solution lessening or relieving the irritability of the follicles and glands of the part. The papules and black spots of acne yield sometimes very rapid to the application of the alcoholic solution of hydrastine hydrochlorate. Acne rosacea and seborrhœa oleosa or the greasy state of the skin so often seen in the face of young women have in several instances improved much on an application of an aqueous solution of this drug, or a mixture of the salts with a fatty substance in the proportion of from five to twenty grains to the ounce.

The ointment of hydrastine hydrochlorate, the salt being incorporated in the fat in from ten to sixty grains to the ounce, has proved a most excellent application in some cases of subacute and chronic eczema; the thickened and irritable state of the skin in the latter condition subsiding at times very rapidly

on its application. It has also been serviceable in some scrofulous and varicose ulcers used in the form of an ointment. The good results so far realized from the topical application of hydrastine hydrochlorate may be illustrated by the following cases in which it has been employed in the clinical service of the Philadelphia Hospital for Skin Diseases.

Acne.—Robert T. æt 17. Forehead, cheeks and chin covered with small red papules associated with black points—acne punctata—and papulo-pustules, digestion feeble, bowels torpid. Ten drop doses of the fluid extract of hydrastis were given three times daily before meals and the face was sponged night and morning with an aqueous solution of hydrastine hydrochlorate containing ten grains of the salt to the ounce. In ten days the patient showed signs of improvement, and in six weeks after being placed under treatment he was discharged cured.

Eczema of the Face.—Anna B. æt 3. Scalp and face covered with thick crusts, which upon removal exposed red raw and infiltrated patches, digestion poor, constipation at times followed with diarrhœa. Half a drop increased to a drop of the fluid extract of hydrastis was administered in milk three times daily with the effect, in course of twelve days, of improving the child's general condition and lessening somewhat the local inflammation. The red and infiltrated patches still remained stubborn, notwithstanding the use of the ordinary ointments. At the end of the second week of the constitutional treatment, one ounce of lard with twenty grains of hydrastine hydrochlorate was used freely over the parts. The red and thickened patches gradually disappeared and in two weeks time from the beginning of the topical application only a slightly desquamating surface remained.

Eczema of the Anus.—James T. æt 32. Had been under treatment at various times with only temporary relief. The margins around the anus was thickened and fissured, many of which extended well into the mucous membrane of the parts. No apparent exciting cause could be detected. The application of the ointment of hydrastine hydrochlorate twenty grains of the salt to the ounce being employed was followed by relief within a few days. Several weeks have now passed and the patient having failed to report has doubtless obtained permanent relief.

Eczema of the Ears.—Mary W. æt 27. The right and left ears were red, somewhat thickened and covered with scales. The skin back of each pinna was in a similar condition with several fissures at their connection with the side of the head. The inflammation of the ears had originally been excited by a dye, and had resisted the usual local remedies. The ointment of hydrastine hydrochlorate, of the same strength as mentioned in the previous case, was used with good effect within six days. The ears in about three weeks had acquired their natural size. The fissures healed quickly, and when last seen, about ten days ago, only a little roughness of the integument was apparent.

Eczema of the Feet.—Mrs. G. æt 36. The dorsal surface of both feet were red, slightly infiltrated, especially about the toes, between which were some well marked fissures. The disease had been in existence for some time and had been caused by using some remedy to remove corns from the feet. At first, a five, and afterward, a ten per cent. ointment of hydrastine hydrochlorate was used which completely removed the disease in from five to six weeks time.

Seborrhœa Sicca of the Scalp.—Wm. S. æt 22. The scalp was caked over with a thick sebaceous secretion, the hair being dry and lustreless. The disease had followed after typhoid fever, the patient at the time of examination was weak and poorly nourished. Cod liver oil in large doses soon improved the systemic condition, but the local trouble continued the same. The parts were sponged once daily with an alcoholic solution of hydrastine hydrochlorate, thirty grains of the salt being employed to the ounce with the effect of removing within eight or ten days all the crusts and scales, and after some three weeks topical application but a slight evidence of the disease existed.

Inflammation of the hair follicles of the Beard.—Thomas R. æt 24. The upper lip was the seat of many pustules and papules, especially around the margin of the anterior nares. Two grain doses of the iron iodide was administered and a ten per cent. hydrastine hydrochlorate ointment applied to the parts, brought relief within six or eight days, the patient then disappeared and has not since reported.

Seborrhœa Oleosa.—Maggie C. æt 19. Forehead, cheeks and nose slightly red and very greasy.

Many of the follicles of the parts were plugged with comedones, and the skin in patches presented even a dirty hue. A uterine cause which excited the disease had been removed by one of the physicians at a general hospital, but the local condition, although lessened by the previous treatment, continued annoying. An aqueous solution of first five and afterward twenty grains of hydrastine hydrochlorate to the ounce lessened the poured out oily fluid and improved decidedly the deformity of the skin in about two weeks time. Patient has since ceased her visits to the hospital and perhaps has concluded she is now cured.

Hyperidrosis.—Mrs. L. æt 39. Applied for the relief of excessive sweating from the arm pits, which had been very annoying for some time. Health good and local trouble could not be traced to any constitutional cause. The frequent use of an aqueous solution containing thirty grains of hydrastine hydrochlorate to the ounce proved an effective application within a few weeks time.

Ulcers.—Carrie H. æt 13. Had two small ulcers, one on the right and the other on the left side beneath the inferior maxillary from broken down lymphatic glands. The floor and margins of the ulcers were covered with indolent granulations and with an unhealthy and scanty pus. Constitutional treatment improved without removing the ulcers. A ten increased to a twenty per cent. hydrastine hydrochlorate ointment healed them completely in a little over one month's time.

Hydrastine hydrochlorate from the cases just cited and others now improving under its use will no doubt prove a valuable topical application, especially in diseases of the skin. Its stimulant and astringent properties may make it available, not only in the affections alluded to, but also in many others. From present experience it is better adapted for use in diseases in which the inflammation is not too active, more particularly in the subacute and chronic stages. Precautions should be exercised in using it, on an acute eruption and if employed the solution or ointment should be very weak otherwise the active stimulant and astringent effect of the salt may increase instead of diminish the disease. It is better and much more effective even in those diseases in which it is indicated not to use too strong a solution or ointment in beginning the application to the skin.

ACTION OF HYDRASTINE HYDROCHLORATE ON THE GENITO-URINARY MUCOUS MEMBRANES—(Written for this publication by Prof. F. W. LANGDON, M. D., of the Miami Medical College of Cincinnati).—Prominent amongst the features which have characterized the progress of modern medicine are those improvements in pharmaceutical chemistry whereby we are enabled to obtain, in concentrated form, the active principles of various vegetable remedies, such as morphine, atropine, quinine, strychnine, piperine, theine, cocaine, etc. We have another instance of this dominion of mind over matter in the preparation which forms the subject of the present observations, viz: The Hydrochlorate of Hydrastine, prepared from the white alkaloid of the well-known plant, *Hydrastis canadensis*.

At the request of the Messrs. Lloyd, I have instituted a series of clinical experiments with this preparation, somewhat limited as regards time and number, but sufficient to demonstrate the fact that the drug in this form possesses the power of influencing favorably certain morbid conditions of the secreting structures of the male urethra. I have used the drug, as an injection only, in the strength of one-half grain to three grains to the ounce of distilled water.

To sum up, briefly, the results of this series of observations, we may classify the cases under three heads, namely:

1.—Acute Gonorrhœa. Here the use of an injection containing one to two grains to the ounce, *after* the subsidence of the first acute symptoms, swelling, pain, etc., arrested the discharge in a few days in several cases. This, however, as is well known, is so common a result of the use of many other remedies (and even, at times, occurs spontaneously, if patients are to be believed) that its significance may readily be overestimated. The fact, however, that it has been uniformly successful in even a small number of cases (six) is worthy of note.

2.—Gleet dependent on stricture or localized ulceration. Here, as might be expected, its use was attended by unsatisfactory results, as would be any measures short of treating the actual lesion. While a slight improvement seemed to follow its use in some of these cases, in others it exerted a decidedly irritant action, even in the strength of one grain to the ounce.

3.—Gleet dependent on a relaxed condition of the urethral mucous membrane purely functional; the discharge a mere weeping, almost watery in character—a *true catarrh*, in fact. It is in these cases that the drug seems to exert a most favorable influence, producing immediate improvement and final cure in troublesome cases which had resisted the variety of men and measures to which they are usually subjected. Its use, however, requires caution as regards the strength of solution. While an injection of two to three grains to the ounce of distilled water produces the best results in some, others manifest an immediate increase of irritation and discharge upon using even a one-grain solution; so that, to begin with, a half-grain solution is sufficient for most cases, to be gradually increased according to indications.

The drug certainly deserves further attention at the hands of the profession.

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* In making these references, care has been taken to capitalize the specific name only when capitalized in the original work. A dash after the name indicates that no authority is given for it.

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